US 20230416363A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2023/0416363 A1**

Lu et al. (43) **Pub. Date: Dec. 28, 2023**

(54) **ANTI-PD-1 ANTIBODIES AND FUSION PROTEINS**

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(21) Appl. No.: **18/011,878**

(22) PCT Filed: **Jun. 23, 2021**

(86) PCT No.: **PCT/US2021/038740**

§ 371 (c)(1),
(2) Date: **Dec. 21, 2022**

Related U.S. Application Data

(60) Provisional application No. 63/111,459, filed on Nov. 9, 2020, provisional application No. 63/043,114, filed on Jun. 23, 2020.

Publication Classification

(51) **Int. Cl.**

C07K 16/28	(2006.01)
C07K 14/715	(2006.01)
C12N 15/63	(2006.01)
A61P 35/00	(2006.01)

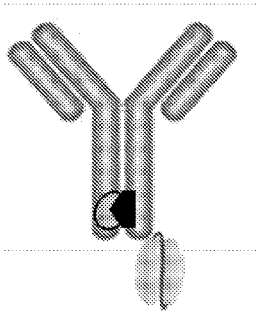
(52) **U.S. Cl.**

CPC ***C07K 16/2818*** (2013.01); ***C07K 14/7155*** (2013.01); ***C12N 15/63*** (2013.01); ***A61P 35/00*** (2018.01); *C07K 2317/565* (2013.01); *C07K 2317/31* (2013.01); *C07K 2317/526* (2013.01)

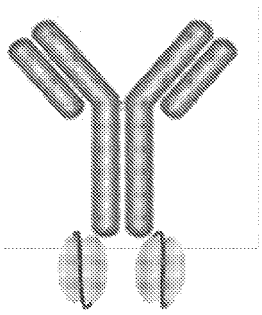
(57) **ABSTRACT**

Provided herein are recombinant antibodies, antigen-binding fragments, and fusion proteins thereof useful for binding to and inhibiting programmed death 1 (PD-1), nucleic acid molecules encoding the same and therapeutic compositions thereof, as well as methods of using such antibodies, including the methods for enhancing T cell and NK cell function to increase cell and cytokine mediated immunity and methods of treatment of various immune dysfunction related disorders including cancer and infectious diseases.

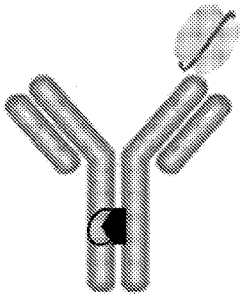
Specification includes a Sequence Listing.



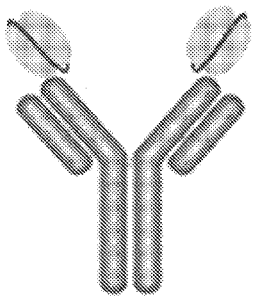
1C-antibody/IL-15



2C-antibody/IL-15



1N-antibody/IL-15



2N-antibody/IL-15

		HCDR1 (SEQ ID NO:)	HCDR2 (SEQ ID NO:)	HCDR3 (SEQ ID NO:)	SEQ ID NO:
19B6HC	QVQLVQSGAEVKKPGASVKVSCKAS	GYTFTGYYMH (1)	WVRQAPGQGLEWMG IINPSGGSTSYAQKFQG (2)	RVTMTRDTSTSTVYMELSSLRSEDTAVYYCAK TAGYDWLPSGLGMDV (3)	WGQGTTVTVSS 4
19B10HC	EVQLLESGGGLVQPGGSLRLSCAAS	GFTFSSYAMH (5)	WVRQAPGKGLEWVS GISNSGGNTYYADSVKG (6)	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR DNYYYYMDV (7)	WGKGTTVTVSS 8
23A8HC	EVQLLESGGGLVQPGGSLRLSCAAS	GFTFSSSAMH (9)	WVRQAPGKGLEWVS GISGSGSSTYYADSVKG (10)	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR DNNYYYYMDV (11)	WGKGTTVTVSS 12
23A11HC	QVQLVQSGAEVKKPGSSVKVSCKAS	GYTFTDYSLH (13)	WVRQAPGQGLEWMG EVIPMFDTAYYAQTFQG (14)	RVTITADESTSTAYMELSSLRSEDTAVYYCAR EPFTMVRGGRYYYYGMDV (15)	WGQGTTVTVSS 16
23H9HC	QVQLVQSGAEVKKPGSSVKVSCKAS	GGTFSSSVIS (17)	WVRQAPGQGLEWMG GIIPIFGTANYAQKFQG (18)	RVTITADESTSTAYMELSSLRSEDTAVYYCAR EGLGCSGGSCYSGYYYGMDV (19)	WGQGTTVTVSS 20
24H9HC	EVQLLESGGGLVQPGGSLRLSCAAS	GFTFSSYWMS (21)	WVRQAPGKGLEWVS AISGSGGSTYYADSVKG (22)	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAS SPLQWVDV (23)	WGQGTTVTVSS 24

		LCDR1 (SEQ ID NO:)	LCDR2 (SEQ ID NO:)	LCDR3 (SEQ ID NO:)	SEQ ID NO:
19B6LC	DIQMTQSPSSLSASVGDRVTITC	RASQSINSWLA (25)	WYQQKPGKAPKLLIY YASSLQS (26)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGYSVPLS (27)	FGQGTKLEIK 28
19B10LC	DIQMTQSPSSLSASVGDRVTITC	RASQSVSTWLA (29)	WYQQKPGKAPKLLIY AASNLET (30)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQTYSTPYT (31)	FGQGTKLEIK 32
23A8LC	DIQMTQSPSSLSASVGDRVTITC	RASQSIGTWLA (33)	WYQQKPGKAPKLLIY AASTLRS (34)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQSYSTPYT (35)	FGQGTKLEIK 36
23A11LC	DIQMTQSPSSLSASVGDRVTITC	RASQNINKNLN (37)	WYQQKPGKAPKLLIY DASNLQS (38)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QHSET (39)	FGQGTKVEIK 40
23H9LC	DIVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD (41)	WYLQKPGQSPQLLIY LSSHRAS (42)	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC MQGAHWPYT (43)	FGQGTKVEIK 44
24H9LC	DIQMTQSPSSLSASVGDRVTITC	RASQGISSWLA (45)	WYQQKPGKAPKLLIY SASSLQS (46)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQANSFPFT (47)	FGPGTKVDIK 48

FIG. 1A

Light chain of 23H9 and 23H9 variants

		LCDR1 (SEQ ID NO:)		LCDR2 (SEQ ID NO:)		LCDR3 (SEQ ID NO:)	SEQ ID NO:
23H9LC	DIVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LSSHRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQGAHWPYT	FGQGTKVEIK 44
		(41)		(42)		(43)	
31B1LC	DIVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	EASSLHS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQGTHWPYT	FGQGTKVEIK 51
		(41)		(49)		(50)	
33C4LC	DIVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	EASSLHT	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQGSHWPYT	FGQGTKLEIK 54
		(41)		(52)		(53)	
33G8LC	DIVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	QASTLGS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQGTHWPYT	FGQGTKLEIK 57
		(41)		(55)		(56)	
34C1LC	DIVMTQSPLSLPVTPGEPASISC	RSSESLLYSNGNTYLD	WYLQKPGQSPQLLIY	EVSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQGTRWPYT	FGQGTKVEIK 61
		(58)		(59)		(60)	
Motif	DIVMTQSPLSLPVTPGEPASISC	RSSX$_1$SLLX$_2$SNGX$_3$X$_4$YLD	WYLQKPGQSPQLLIY	X$_5$X$_6$SX$_7$X$_8$X$_8$X$_{10}$	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQGX$_{11}$X$_{12}$WPYT	FGQGTKVEIK 65
		(62)		(63)		(64)	

FIG. 1B

Light chain of 24H9 and 24H9 variants

		LCDR1 (SEQ ID NO:)		LCDR2 (SEQ ID NO:)		LCDR3 (SEQ ID NO:)	SEQ ID NO:
24H9LC	DIQMTQSPSSLSASVGDRVTITC	RASQGISSWLA	WYQQKPGKAPKLLIY	SASSLQS	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQANSFPFT	FGPGTKVDIK 48
		(45)		(46)		(47)	
32A11LC	DIQMTQSPSSLSASVGDRVTITC	RASESISIWLA	WYQQKPGKAPKLLIY	DASNLET	GVPSRFSGSGSGTNFTLTISSLQPEDFATYYC	QQADSFPFT	FGPGTKVDIK 69
		(66)		(67)		(68)	
32D11LC	DIQMTQSPSSLSASVGDRVTITC	RASQSINIWLA	WYQQKPGKAPKLLIY	DASNLET	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQGYSFPFT	FGPGTKVDIK 72
		(70)		(67)		(71)	
32D2LC	DIQMTQSPSSLSASVGDRVTITC	RASQGISRWLA	WYQQKPGKAPKLLIY	EASTLQS	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQAYSFPFT	FGQGTKVDIK 76
		(73)		(74)		(75)	
32G6LC	DIQMTQSPSSLSASVGDRVTITC	RASQSISSWLA	WYQQKPGKAPKLLIY	DASTLQS	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQANSFPFT	FGPGTKVDIK 79
		(77)		(78)		(47)	
38A10LC	DIQMTQSPSSLSASVGDRVTITC	RASQSISTWLA	WYQQKPGKAPKLLIY	DASRLQN	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQGDSFPFT	FGPGTKVDIK 83
		(80)		(81)		(82)	
38A11LC	DIQMTQSPSSLSASVGDRVTITC	RASQSISSWLA	WYQQKPGKAPKLLIY	DASTLQS	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQGNSFPFT	FGPGTKVDIK 85
		(77)		(78)		(84)	
38A4LC	DIQMTQSPSSLSASVGDRVTITC	RASQSISSWLA	WYQQKPGKAPKLLIY	DASNLQT	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQANSFPFT	FGQGTRLEIK 87
		(77)		(86)		(47)	
38A6LC	DIQMTQSPSSLSASVGDRVTITC	RASQDISRWLG	WYQQKPGKAPKLLIY	AASTLQS	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQANSFPFT	FGPGTKLEIK 90
		(88)		(89)		(47)	
38A8LC	DIQMTQSPSSLSASVGDRVTITC	RASESISIWLA	WYQQKPGKAPKLLIY	DASNLET	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQANSFPFT	FGPGTKVDIK 91
		(66)		(67)		(47)	

FIG. 1C

38B1LC DIQMTQSPSSLSASVGDRVTITC RASQSISTWLA WYQQKPGKAPKLLIY EASKLER GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQAYSFPFT FGPGTKVDIK 93
(80) (92) (75)

38B10LC DIQMTQSPSSLSASVGDRVTITC RASQSISTWLA WYQQKPGKAPKLLIS DASTLQT GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGYSFPFT FGPGTKVDIK 95
(80) (94) (71)

38B2LC DIQMTQSPSSLSASVGDRVTITC RASESISSWLA WYQQKPGKAPKLLIY DASSLES GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGDSFPFT FGQGTKLEIK 98
(96) (97) (82)

38C11LC DIQMTQSPSSLSASVGDRVTITC RASQSISRWLA WYQQKPGKAPKLLIS DASTVQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQANSFPFT FGPGTKVDIK 101
(99) (100) (47)

38C6LC DIQMTQSPSSLSASVGDRVTITC RAGRDIWNWVA WYQQKPGKAPKLLIY DASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQANSFPFA FGQGTKVEIK 105
(102) (103) (104)

38G11LC DIQMTQSPSSLSASVGDRVTITC RASEMISRWLA WYQQKPGKAPKLLIY DASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQANSFPFT FGPGTKVDIK 107
(106) (103) (47)

38G9LC DIQMTQSPSSLSASVGDRVTITC RVSQSISWWLA WYQQKPGKAPKLLIY DASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQANSFPFT FGPGTKVDIK 109
(108) (103) (47)

38H3LC DIQMTQSPSSLSASVGDRVTITC RASQGISTWLA WYQQKPGKAPKLLIY EASRLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQAYSFPFT FGPGTKVDIK 112
(110) (111) (75)

39A3LC DIQMTQSPSSLSASVGDRVTITC RASQSISSWLA WYQQKPGKAPKLLIY DASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGDSFPLT FGQGTKVEIK 114
(77) (103) (113)

39B11LC DIQMTQSPSSLSASVGDRVTITC RASQSISSWLA WYQQKPGKAPKLLIY EASRLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQANSFPFT FGPGTKVDIK 115
(77) (111) (47)

39B3LC DIQMTQSPSSLSASVGDRVTITC RASQSIGPWLA WYQQKPGKAPKLLIY DASNLET GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQANSFPFT FGPGTKVDIK 117
(116) (67) (47)

39B6LC DIQMTQSPSSLSASVGDRVTITC RASEDISHWLA WYQQKPGKAPKLLIY DAKDLHP GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQANSFPFT FGQGTRLEIK 120
(118) (119) (47)

39F11LC DIQMTQSPSSLSASVGDRVTITC RASQSISTWLA WYQQKPGKAPKLLIY DASTLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQANSFPFT FGPGTKVDIK 121
(80) (78) (47)

39G5LC DIQMTQSPSSLSASVGDRVTITC RASQNIWWLA WYQQKPGKAPKLLIY DASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQANSFPFT FGPGTKVDIK 123
(122) (103) (47)

39G8LC DIQMTQSPSSLSASVGDRVTITC RASQGISPWLA WYQQKPGKAPKLLIY DASKLET GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQAYSFPFT FGGGTKVEIK 126
(124) (125) (75)

39H11LC DIQMTQSPSSLSASVGDRVTITC RASQSIGTWVA WYQQKPGKAPKLLIY DASNLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQADSFPFT FGQGTKVEIK 128
(127) (38) (68)

39H2LC DIQMTQSPSSLSASVGDRVTITC RASQNIGPWLA WYQQKPGKAPKLLIY DASTLHS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQANSFPFT FGQGTRLEIK 131
(129) (130) (47)

39H7LC DIQMTQSPSSLSASVGDRVTITC RASQSISWWLA WYQQKPGKAPKLLIY DASNLQA GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQAYSFPFT FGPGTKVDIK 134
(132) (133) (75)

Motif DIQMTQSPSSLSASVGDRVTITC $RX_{13}X_{14}X_{15}X_{16}IX_{17}X_{18}WX_{19}X_{20}$ WYQQKPGKAPKLLIY $X_{21}AX_{22}X_{23}X_{24}X_{25}X_{26}$ GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC $QQX_{27}X_{28}SFPX_{29}X_{30}$ FGPGTKVDIK 138
(135) (136) (137)

FIG. 1C (Cont.)

		HCDR1 (SEQ ID NO:)		HCDR2 (SEQ ID NO:)		HCDR3 (SEQ ID NO:)	SEQ ID NO:
R3A9HC	QVQLVQSGAEVKKPGASVKVSCKAS	GHTFTSYYIH (139)	WVRQAPGQGLEWM	GIINPSGGSTSYAQKFQG (140)	RVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR	DRAYGGAGDY (141)	WGQGTLVTVSS 142

		LCDR1 (SEQ ID NO:)		LCDR2 (SEQ ID NO:)		LCDR3 (SEQ ID NO:)	SEQ ID NO:
R3A9LC	DIQMTQSPSSLSASVGDRVTITC	RASQSVGTWLA (143)	WYQQKPGKAPKLLIY	SASTLQS (144)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQSYSAPLT (145)	FGGGTKVEIK 146
m3A7LC	DIQMTQSPSSLSASVGDRVTITC	RASRSISNWLA (147)	WYQQKPGKAPKLLIY	AASSLQS (148)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQSYSAPVT (149)	FGQGTKVEIK 150
m2C1LC	DIQMTQSPSSLSASVGDRVTITC	RASRSISSWLA (151)	WYQQKPGKAPKLLIY	AASSLQS (148)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQSYSIPAT (152)	FGQGTKVEIK 153
m2A1LC	DIQMTQSPSSLSASVGDRVTITC	RASRGISSWLA (154)	WYQQKPGKAPKLLIY	AASSLQS (148)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQSYSPPWT (155)	FGQGTKVEIK 156
m4A5LC	DIQMTQSPSSLSASVGDRVTITC	RASQSIDTWLA (157)	WYQQKPGKAPKLLIY	AASTLES (158)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQSYRAPLT (159)	FGQGTKVEIK 160
m4D1LC	DIQMTQSPSSLSASVGDRVTITC	RASQSISAWLA (161)	WYQQKPGKAPKLLIY	KASSLES (162)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQSYSPPAT (163)	FGGGTKVEIK 164
m3C6LC	DIQMTQSPSSLSASVGDRVTITC	RASQSIDTWLA (157)	WYQQKPGKAPKLLIY	EASSLQG (165)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQSYSTWT (166)	FGQGTKVEIK 167

FIG. 1D

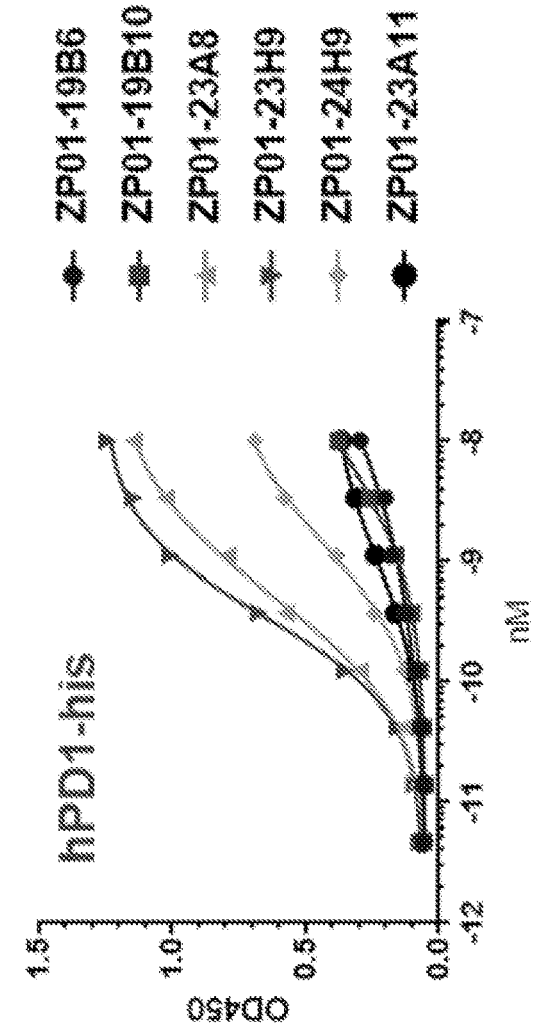

ZP01-19B6
ZP01-19B10
ZP01-23A8
ZP01-23H9
ZP01-24H9
ZP01-23A11
hPD1-his
OD450
nM

Fig. 2B

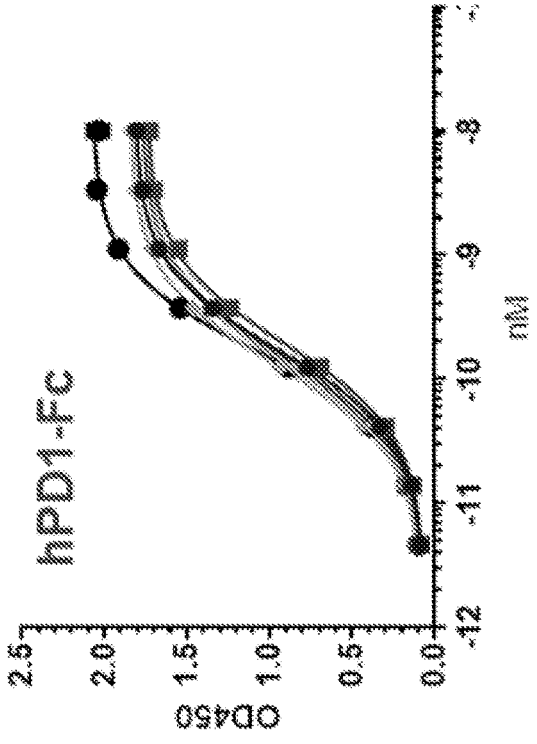

hPD1-Fc
OD450
nM

Fig. 2A

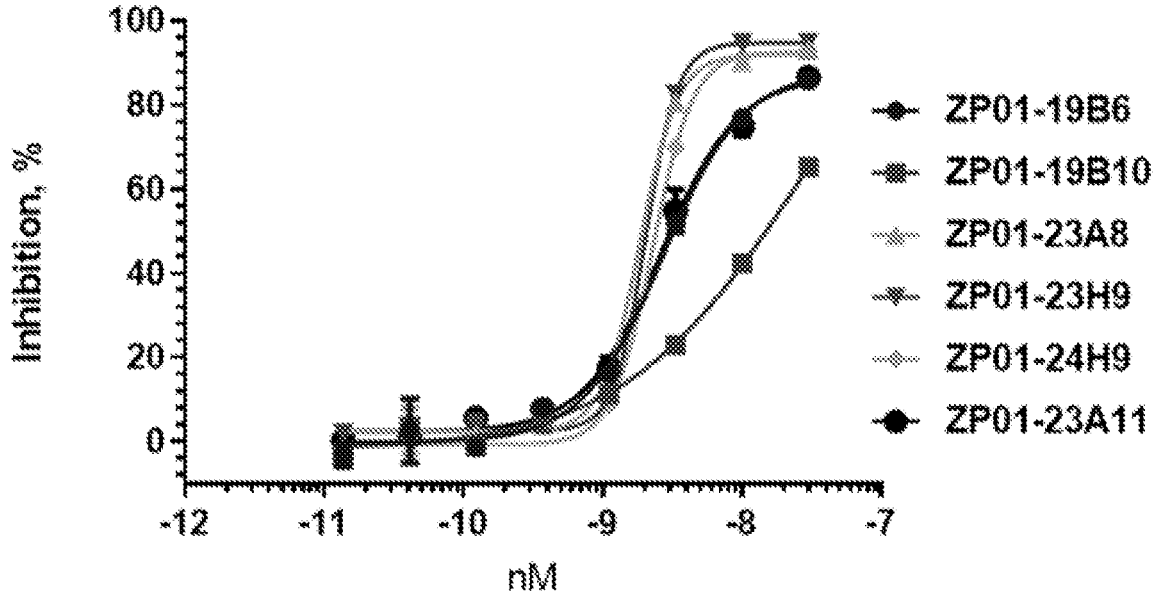

Inhibition, %
100
80
60
40
20
0
-12
-11
-10
-9
-8
-7
nM
ZP01-19B6
ZP01-19B10
ZP01-23A8
ZP01-23H9
ZP01-24H9
ZP01-23A11

Fig. 3

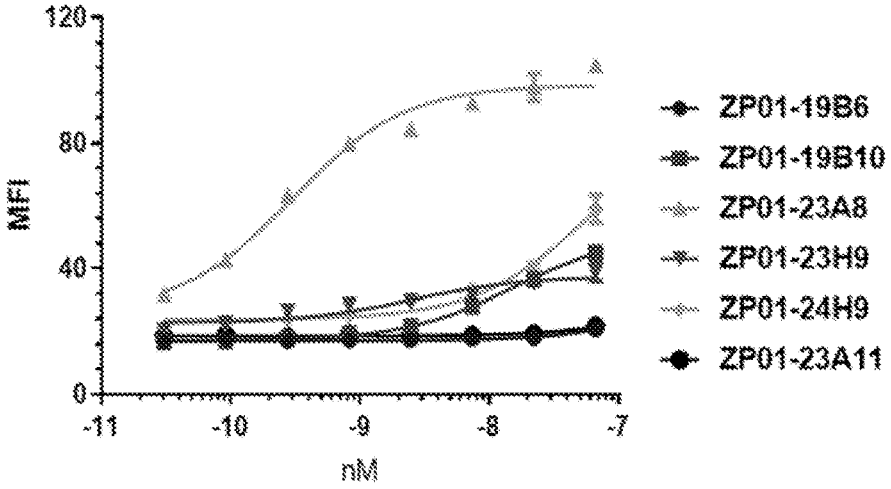


Fig. 4A

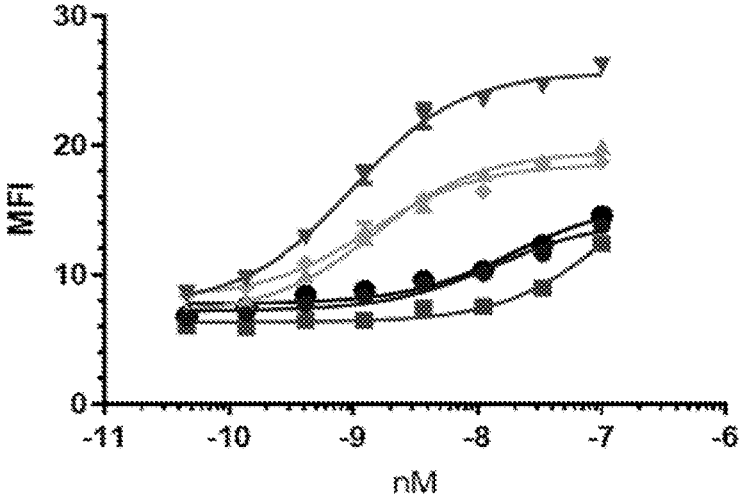


Fig. 4B

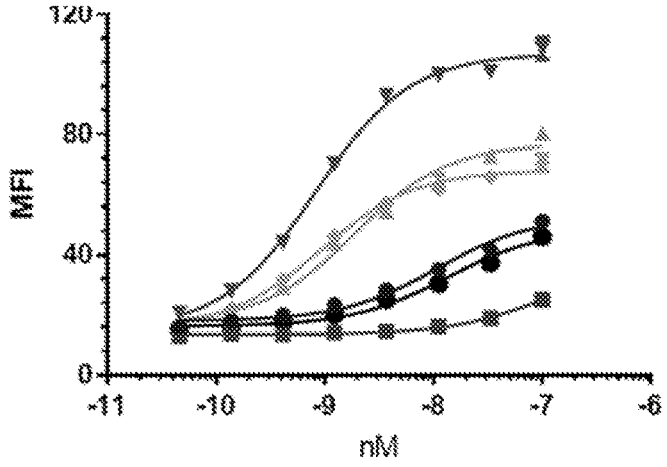


Fig. 4C

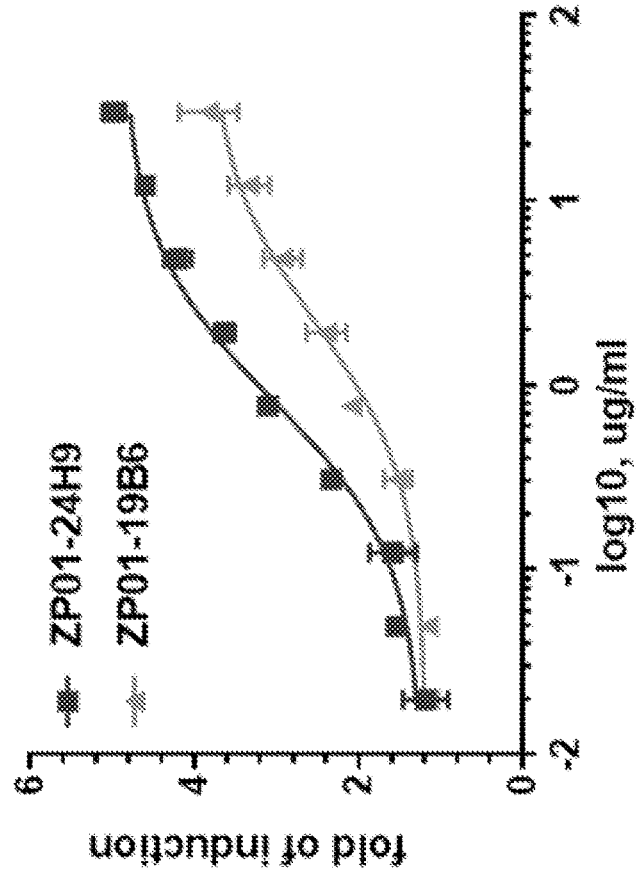

ZP01-24H9
ZP01-19B6
fold of induction
log10, ug/ml

Fig. 5B

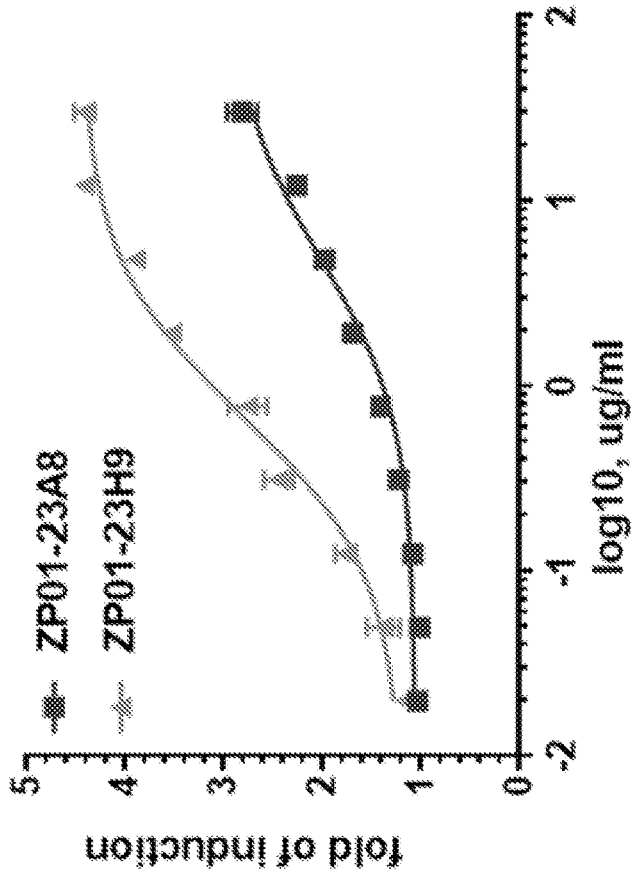

ZP01-23A8
ZP01-23H9
fold of induction
log10, ug/ml

Fig. 5A

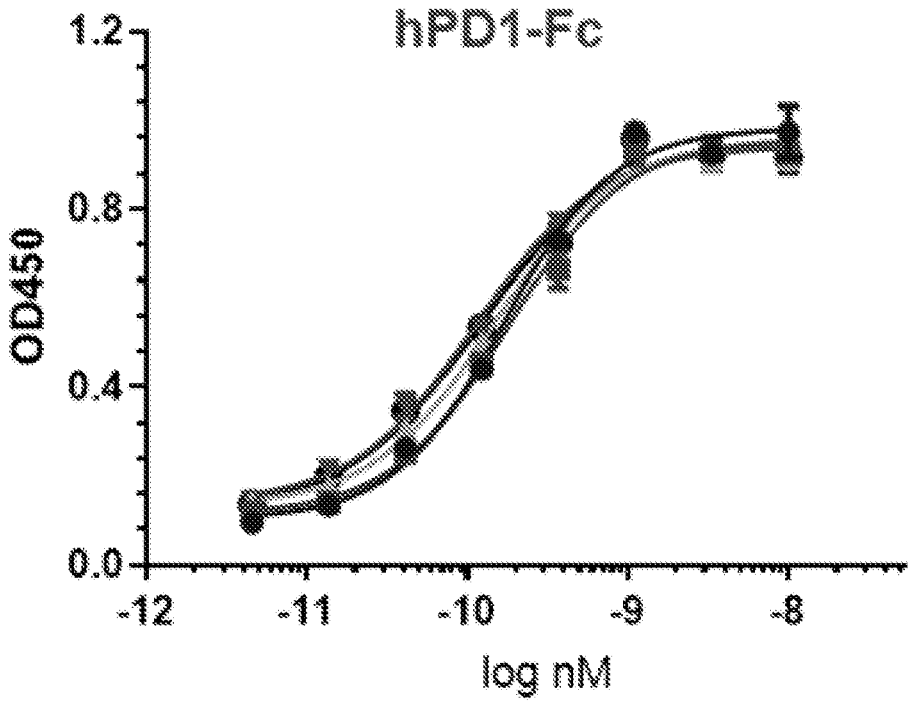

hPD1-Fc
OD450
1.2
0.8
0.4
0.0
-12
-11
-10
-9
-8
log nM

Fig. 6A

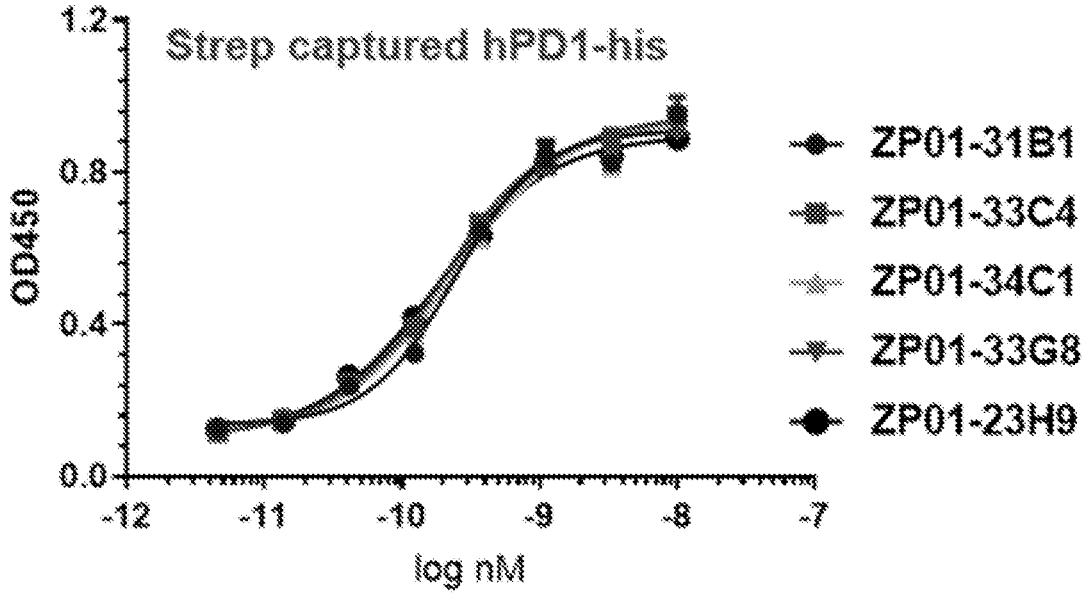

Strep captured hPD1-his
OD450
1.2
0.8
0.4
0.0
-12
-11
-10
-9
-8
-7
log nM
ZP01-31B1
ZP01-33C4
ZP01-34C1
ZP01-33G8
ZP01-23H9

Fig. 6B

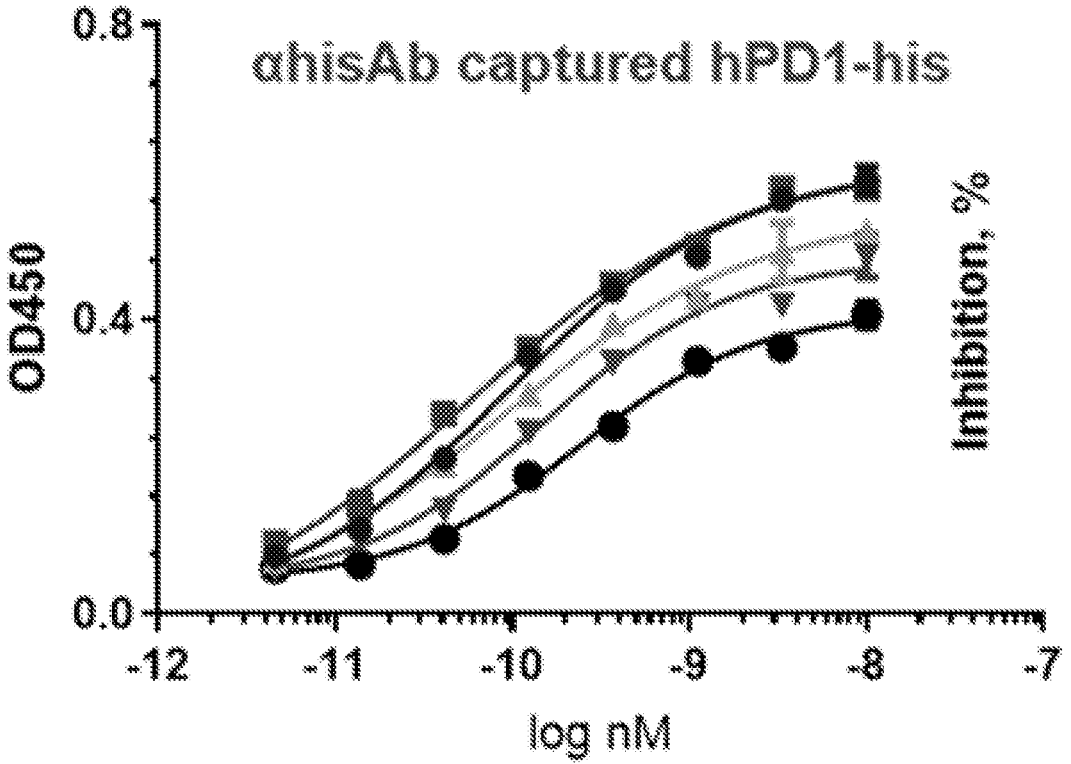

qhisAb captured hPD1-his
OD450
0.8
0.4
0.0
-12
-11
-10
-9
-8
-7
log nM
Inhibition, %

Fig. 6C

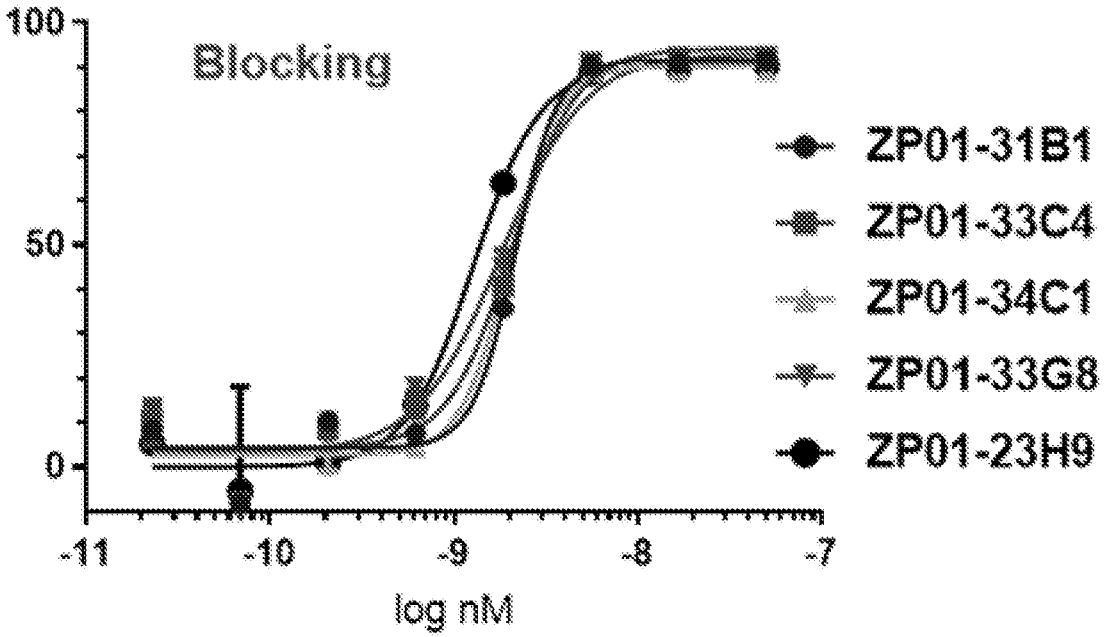

Blocking
100
50
0
-11
-10
-9
-8
-7
log nM
ZP01-31B1
ZP01-33C4
ZP01-34C1
ZP01-33G8
ZP01-23H9

Fig. 6D

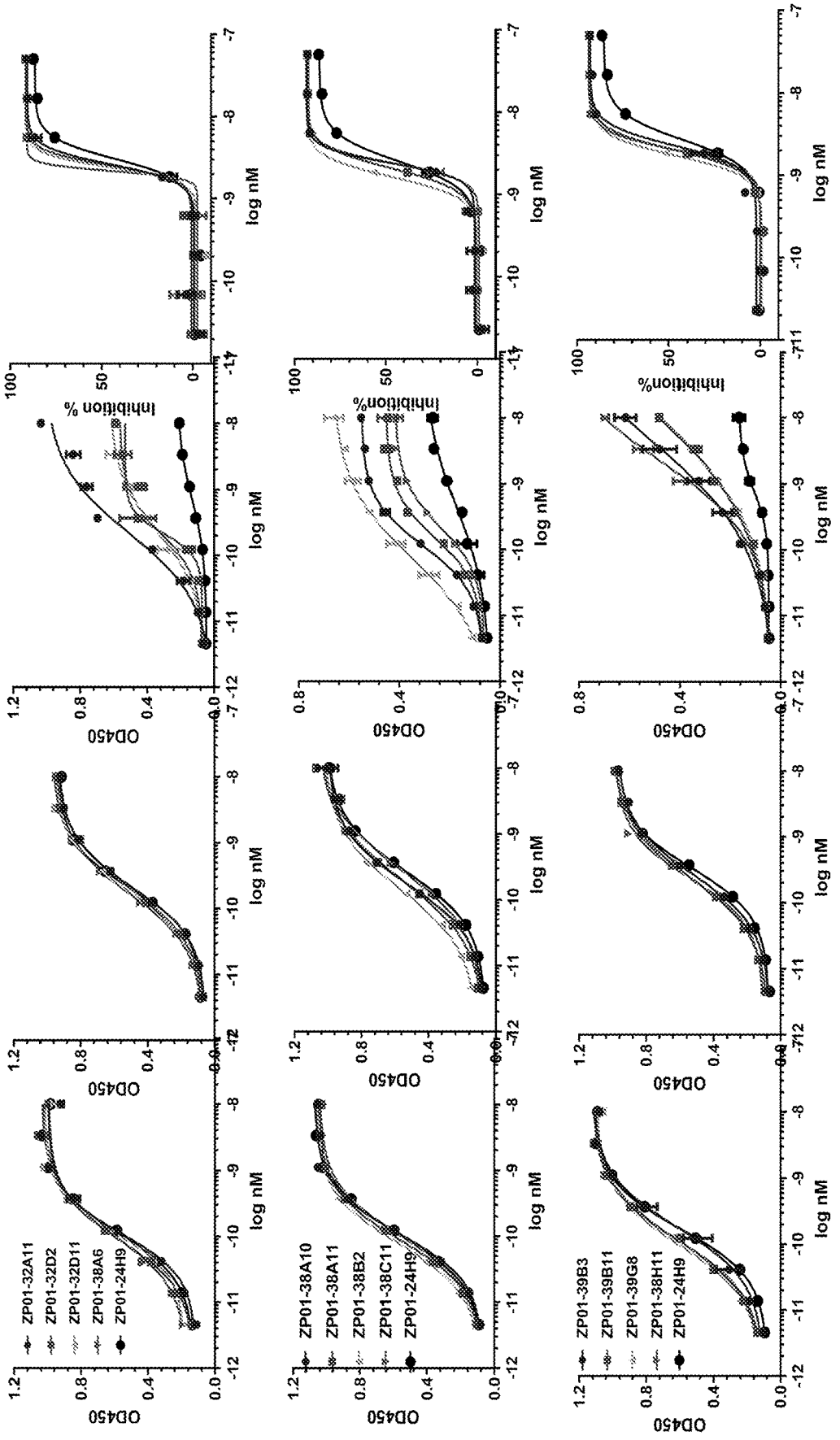

ZP01-32A11
ZP01-32D2
ZP01-32D11
ZP01-38A6
ZP01-24H9
ZP01-38A10
ZP01-38A11
ZP01-38B2
ZP01-38C11
ZP01-24H9
ZP01-39B3
ZP01-39B11
ZP01-39G8
ZP01-38H11
ZP01-24H9
OD450
Inhibition %
log nM

Fig. 7

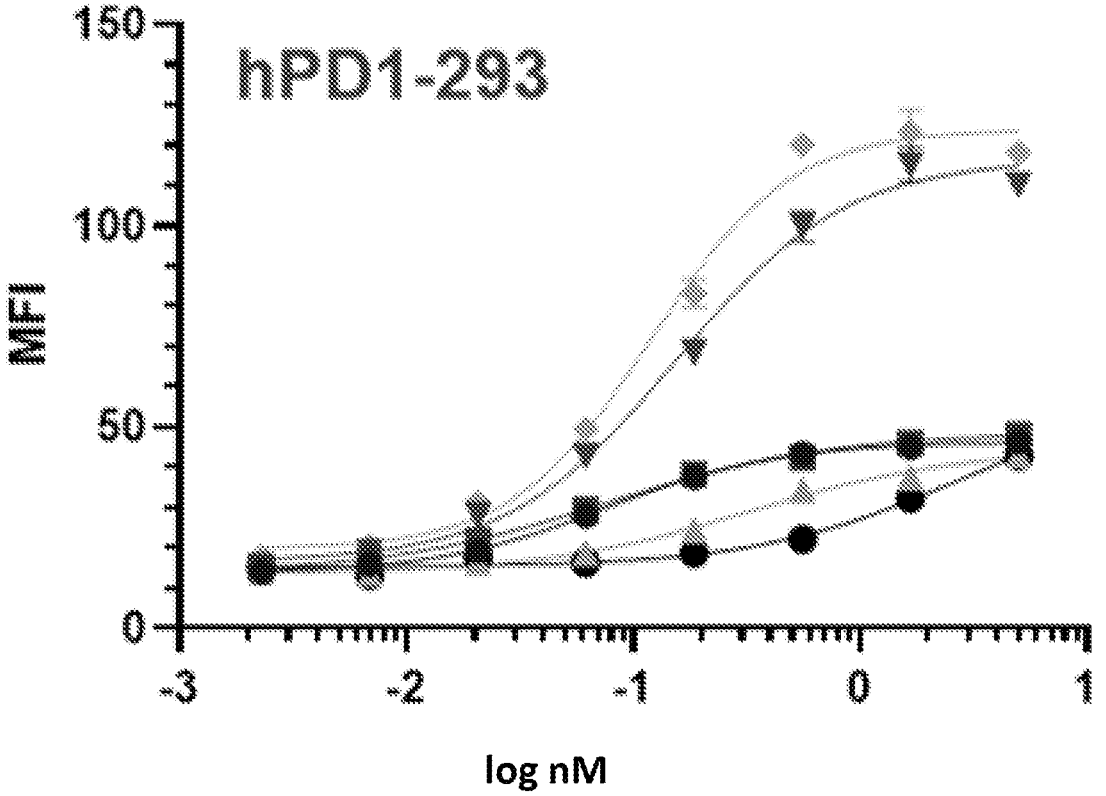

hPD1-293
MFI
150
100
50
0
-3
-2
-1
0
1
log nM

Fig. 8A

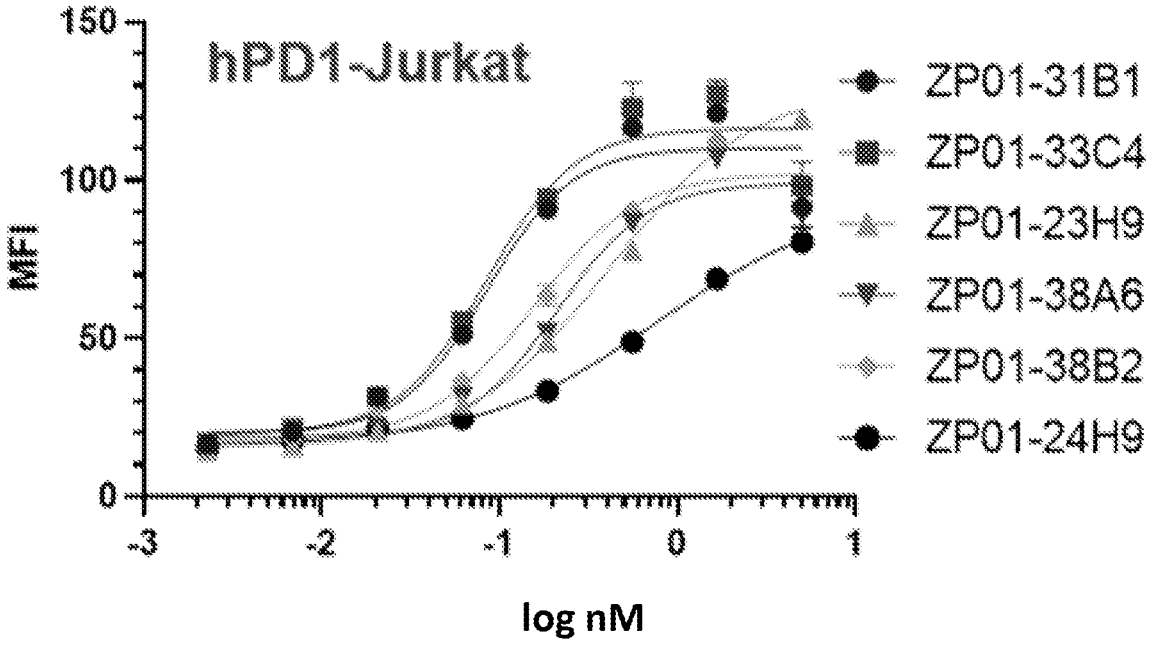

hPD1-Jurkat
MFI
150
100
50
0
-3
-2
-1
0
1
log nM
ZP01-31B1
ZP01-33C4
ZP01-23H9
ZP01-38A6
ZP01-38B2
ZP01-24H9

Fig. 8B

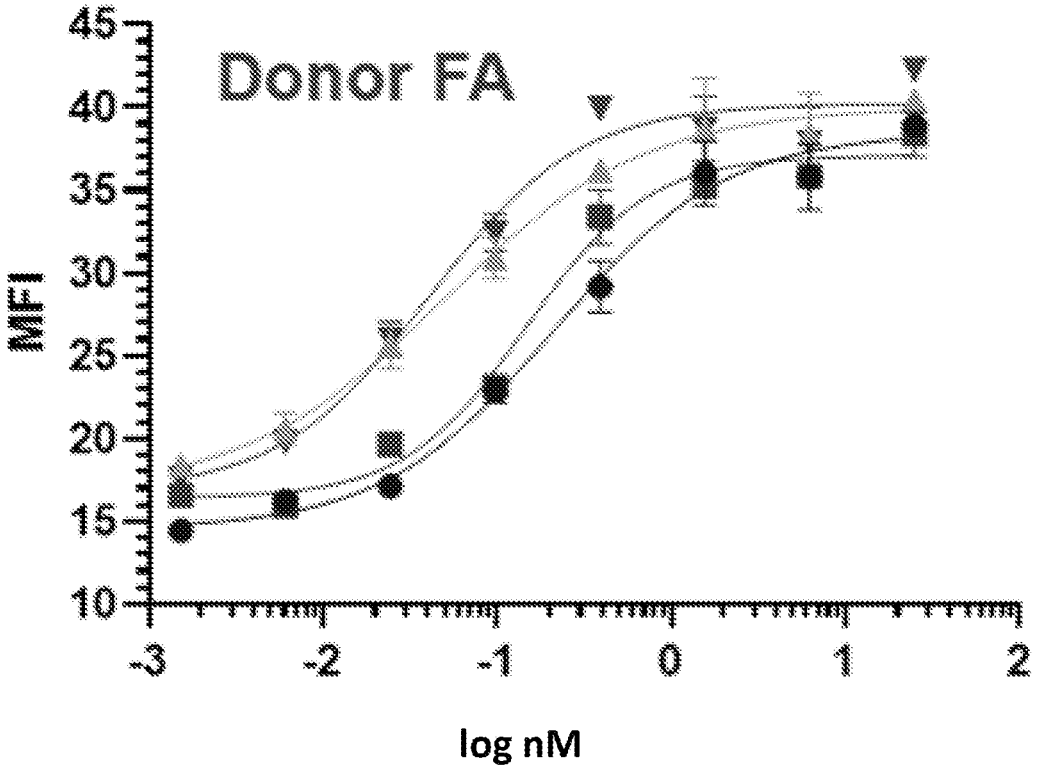

Donor FA
MFI
45
40
35
30
25
20
15
10
-3
-2
-1
0
1
2
log nM

Fig. 8C

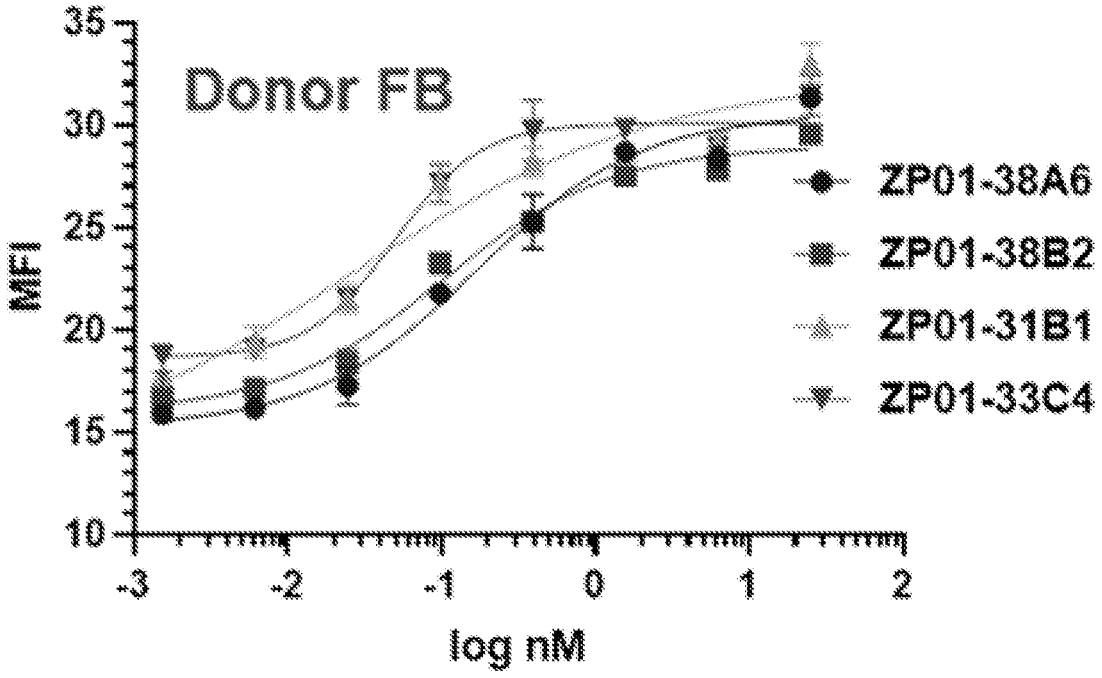

Donor FB
MFI
35
30
25
20
15
10
-3
-2
-1
0
1
2
log nM
ZP01-38A6
ZP01-38B2
ZP01-31B1
ZP01-33C4

Fig. 8D

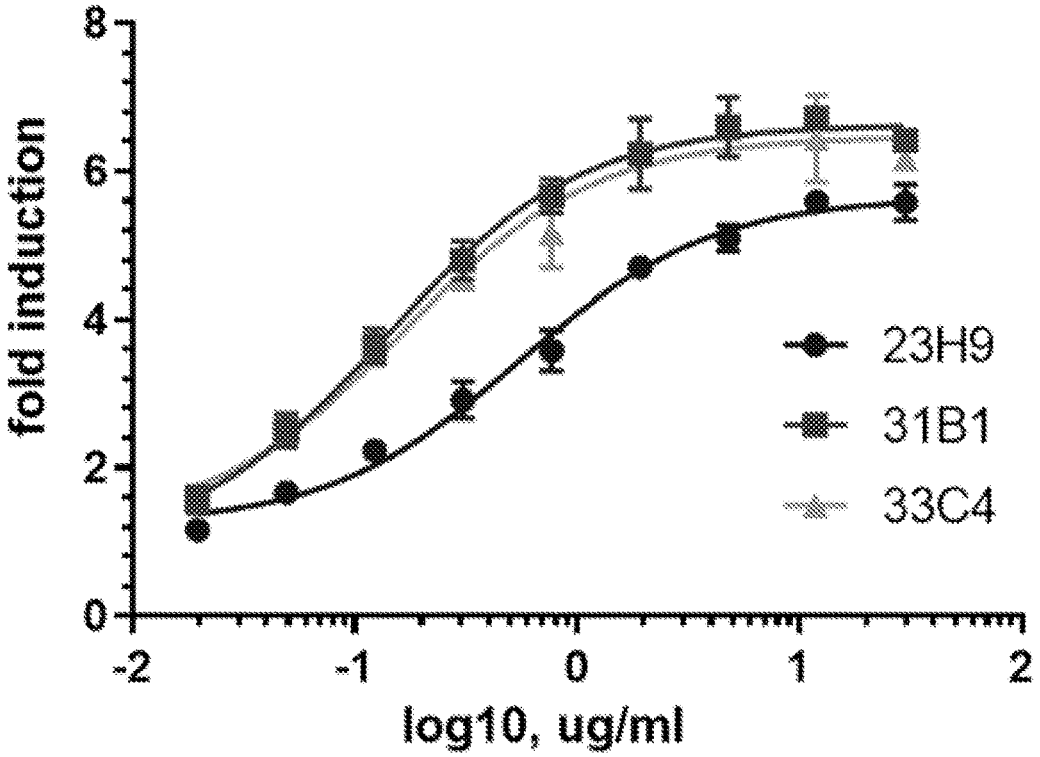

fold induction
log10, ug/ml
23H9
31B1
33C4
0
2
4
6
8
-2
-1
0
1
2

Fig. 9A

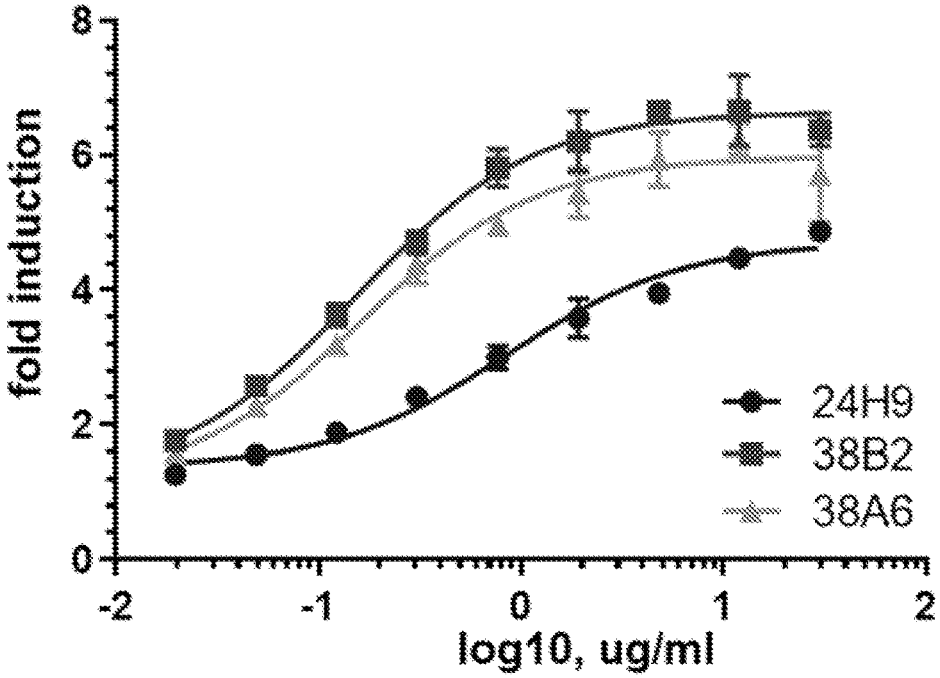

fold induction
log10, ug/ml
24H9
38B2
38A6
0
2
4
6
8
-2
-1
0
1
2

Fig. 9B

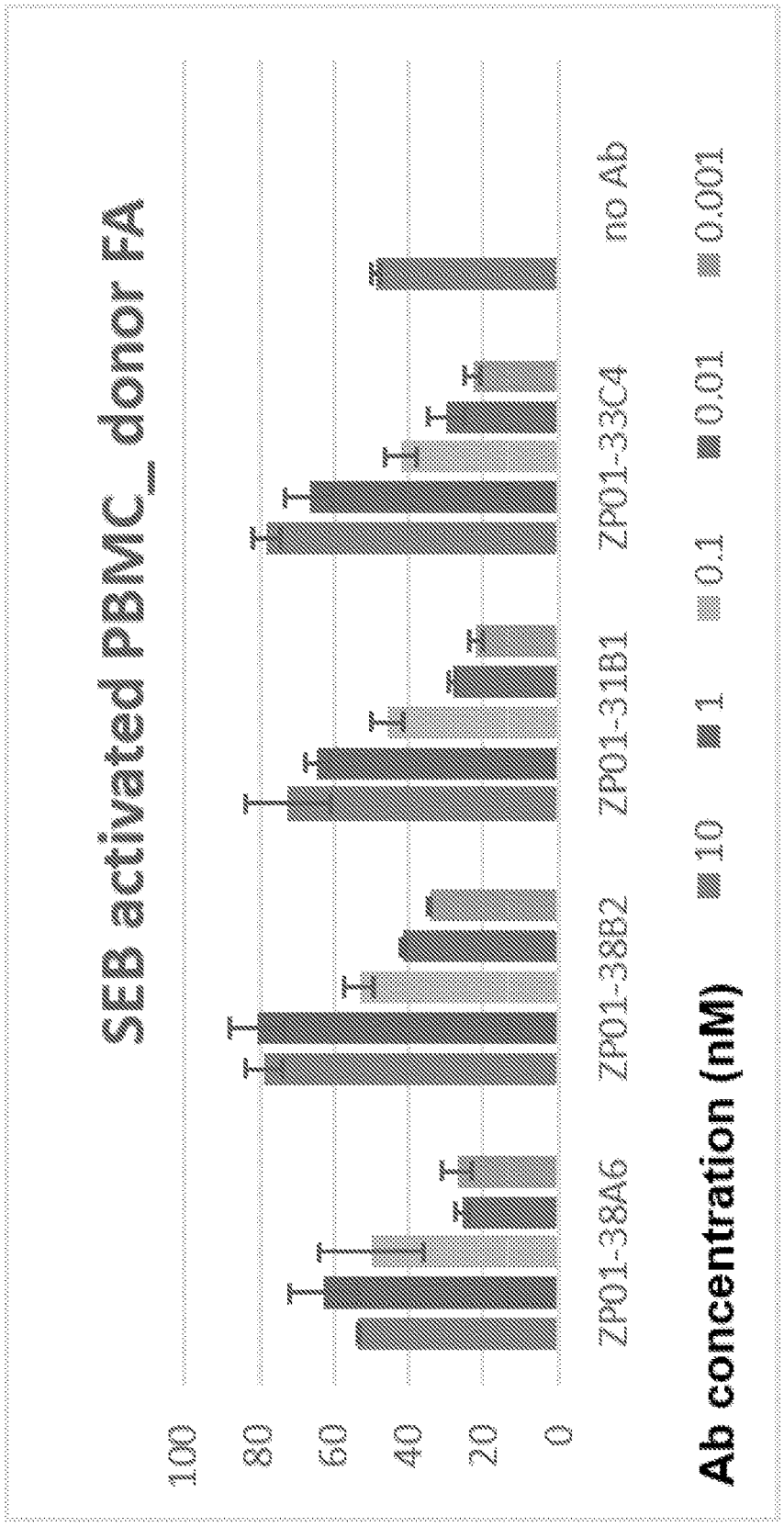

SEB activated PBMC_ donor FA
IL2 concentration pg/ml
100
80
60
40
20
0
ZP01-38A6
ZP01-38B2
ZP01-31B1
ZP01-33C4
no Ab
Ab concentration (nM)
10
1
0.1
0.01
0.001

Fig. 10A

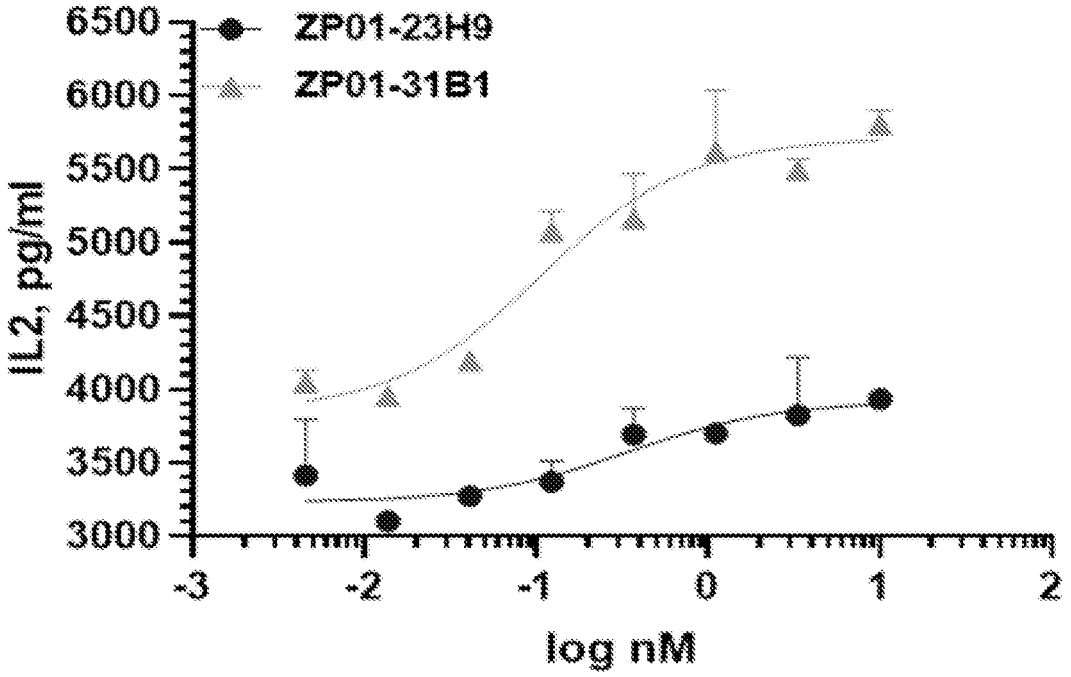


Fig. 10B

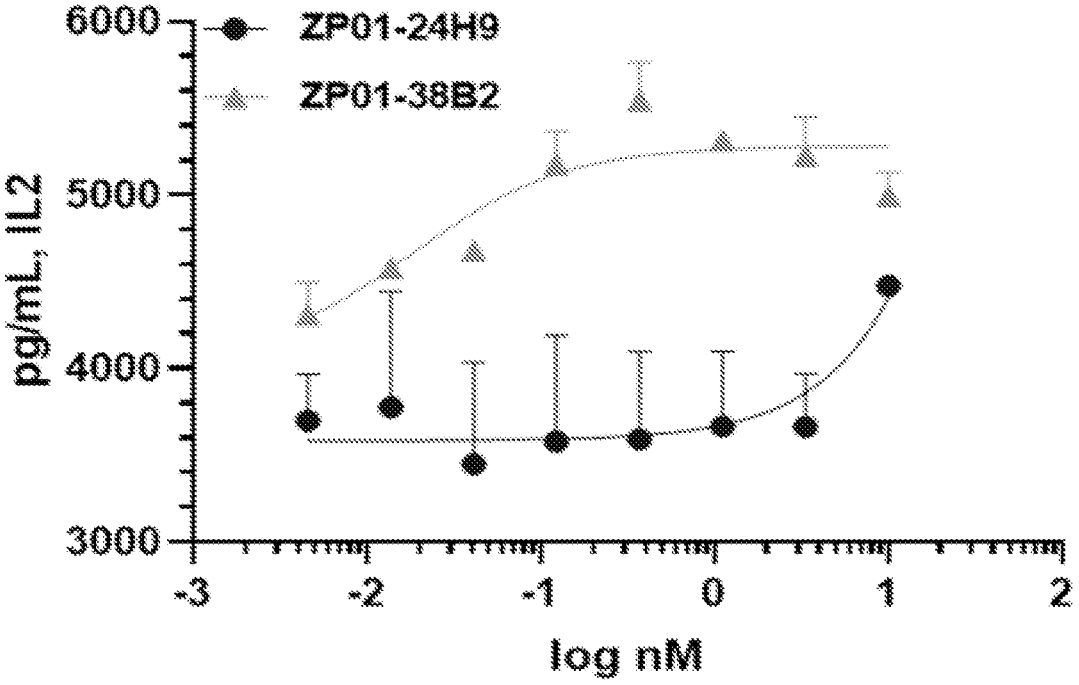


Fig. 10C

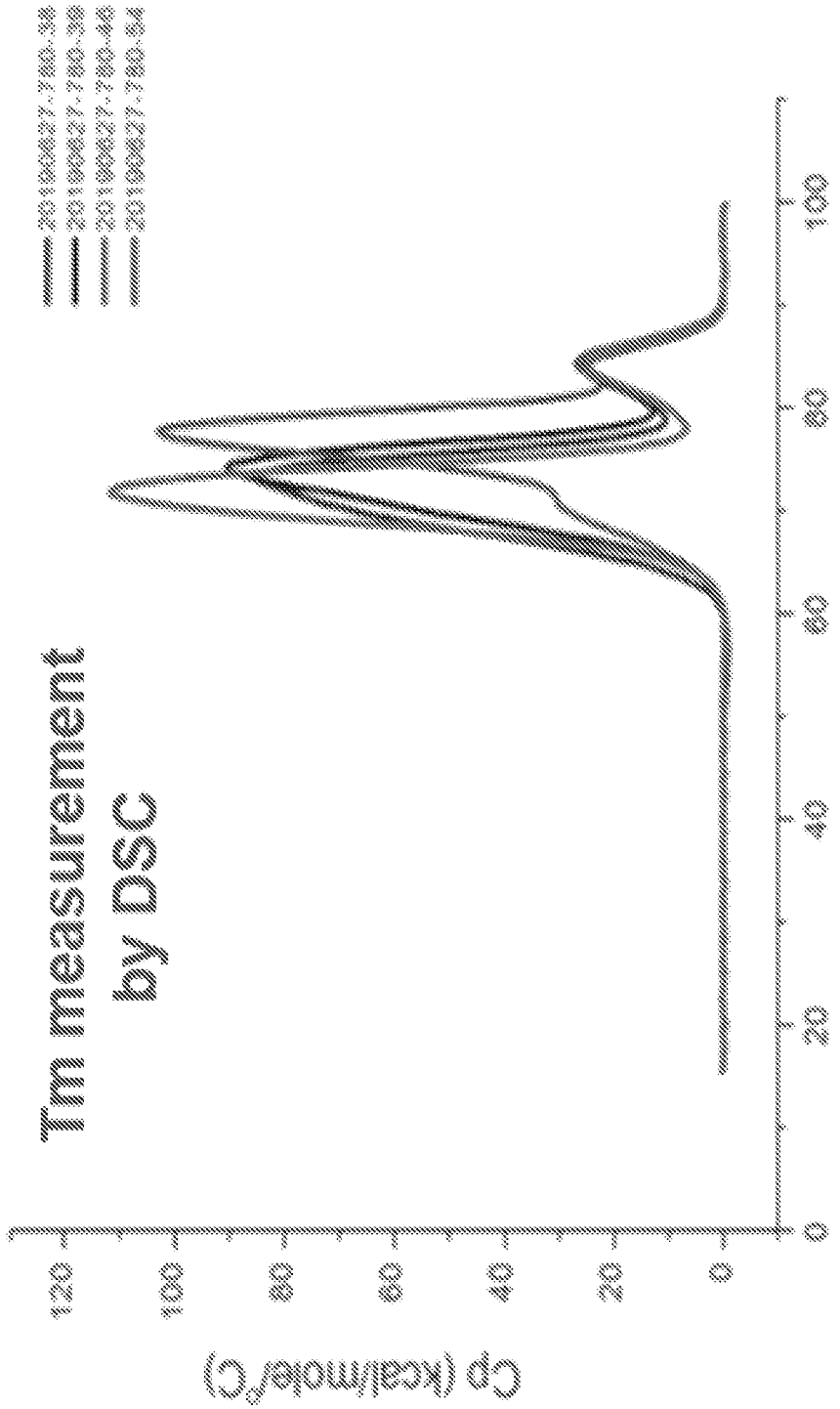

Tm measurement
by DSC
Cp (kcal/mole/°C)
Temperature (°C)
0
20
40
60
80
100
120
20160627-TM0-36
20160627-TM0-39
20160627-TM0-45
20160627-TM0-54

Fig. 11

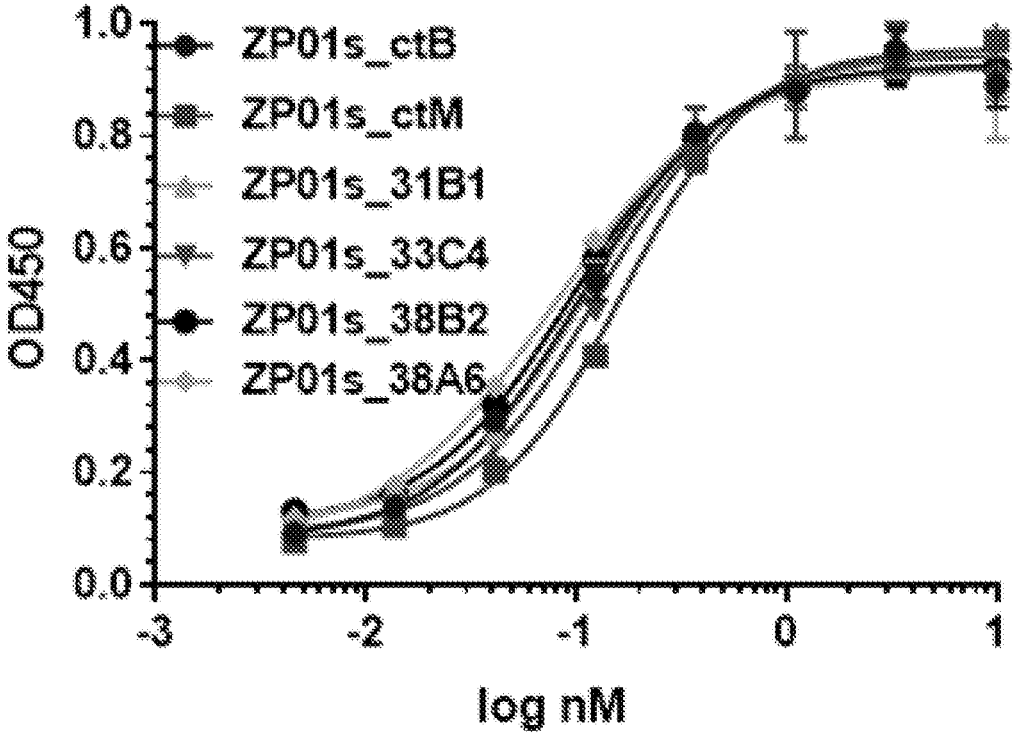


Fig. 12A

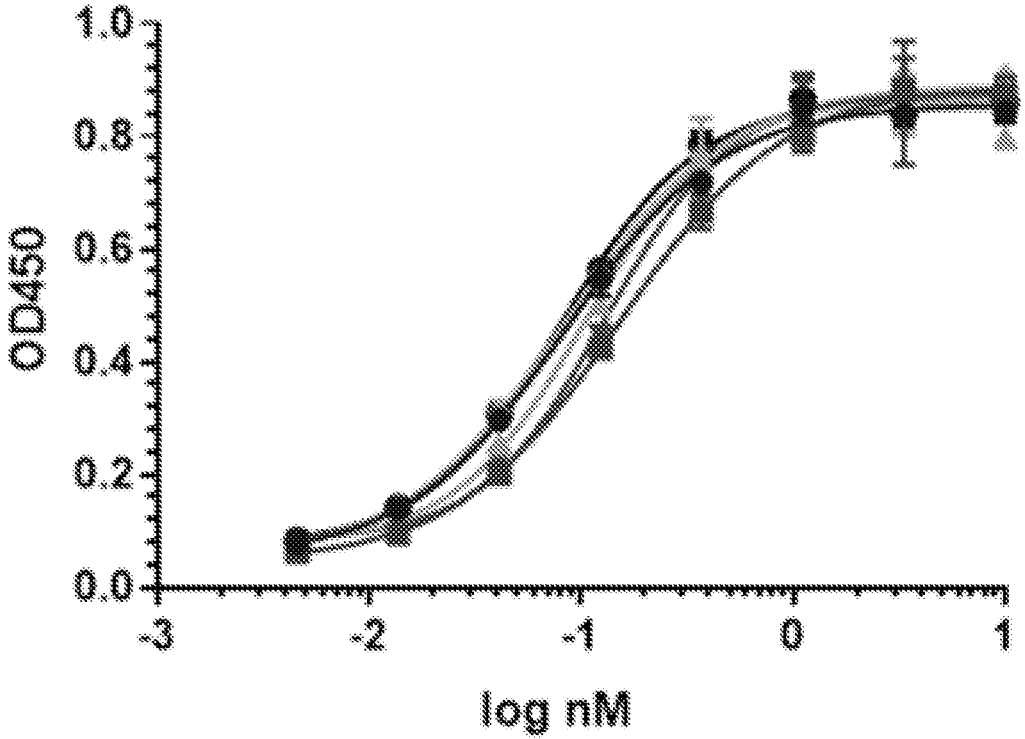


Fig. 12B

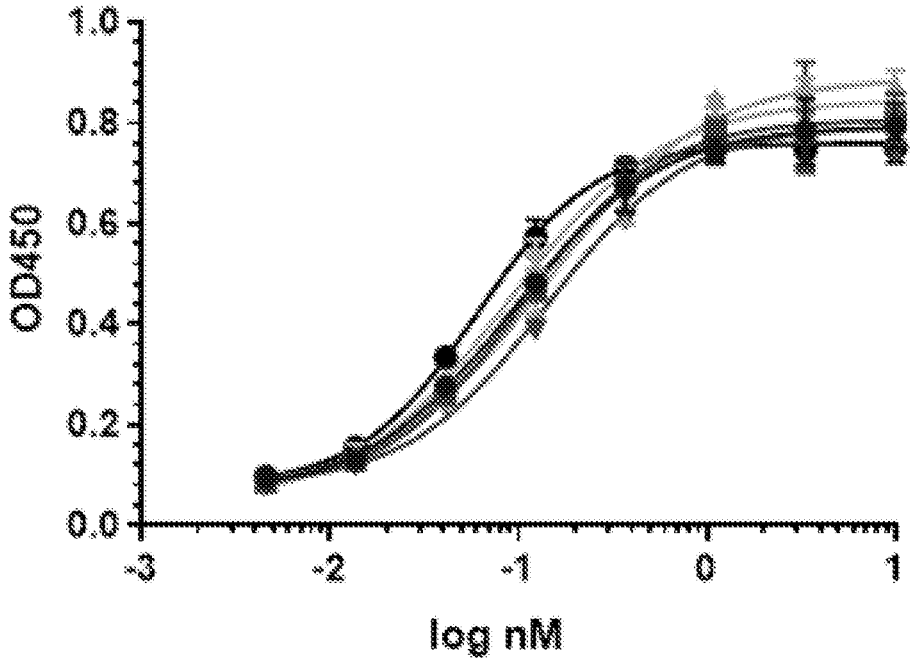


Fig. 12C

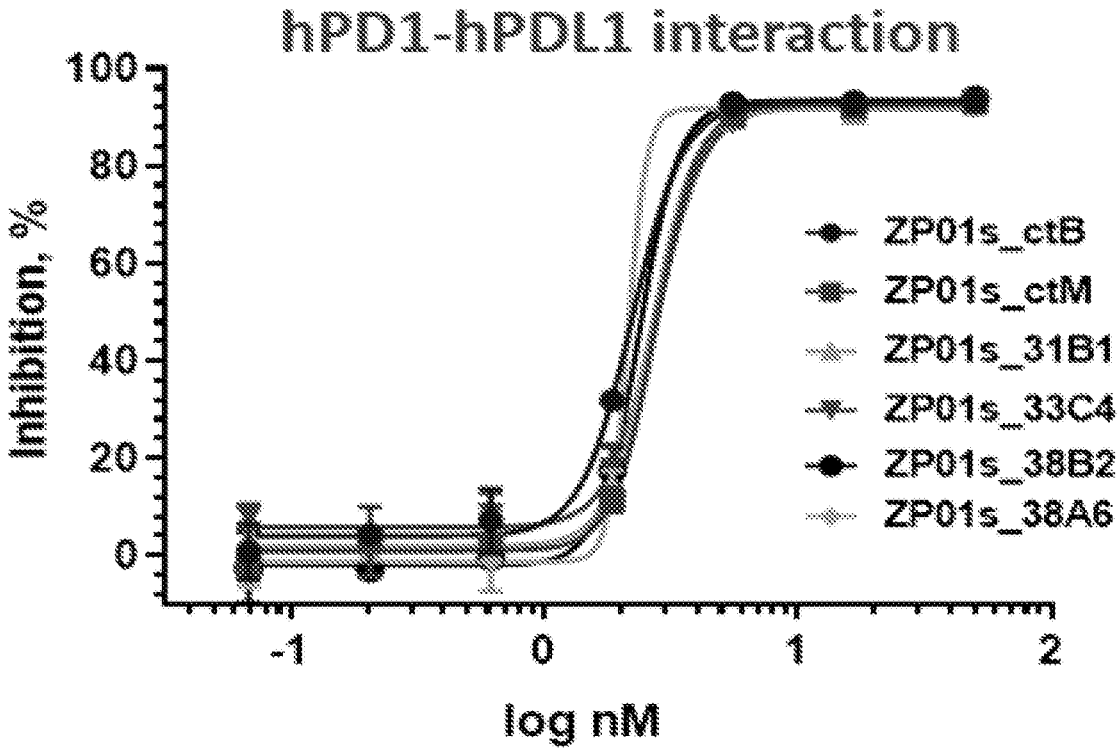


Fig. 12D

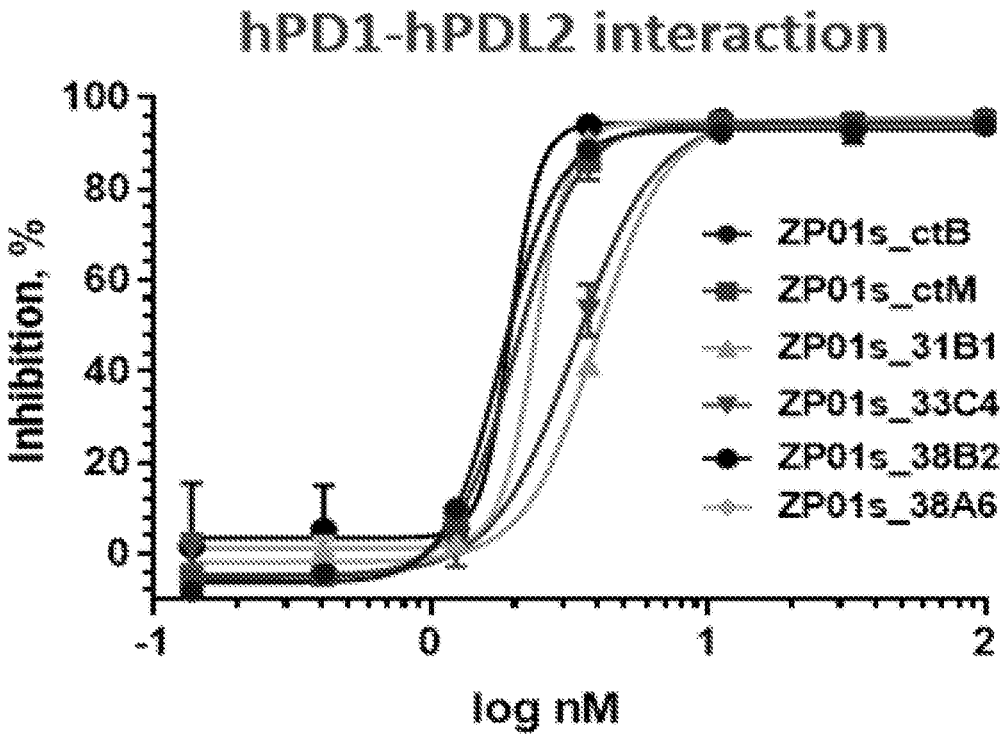

hPD1-hPDL2 interaction
Inhibition, %
100
80
60
40
20
0
-1
0
1
2
log nM
ZP01s_ctB
ZP01s_ctM
ZP01s_31B1
ZP01s_33C4
ZP01s_38B2
ZP01s_38A6

Fig. 12E

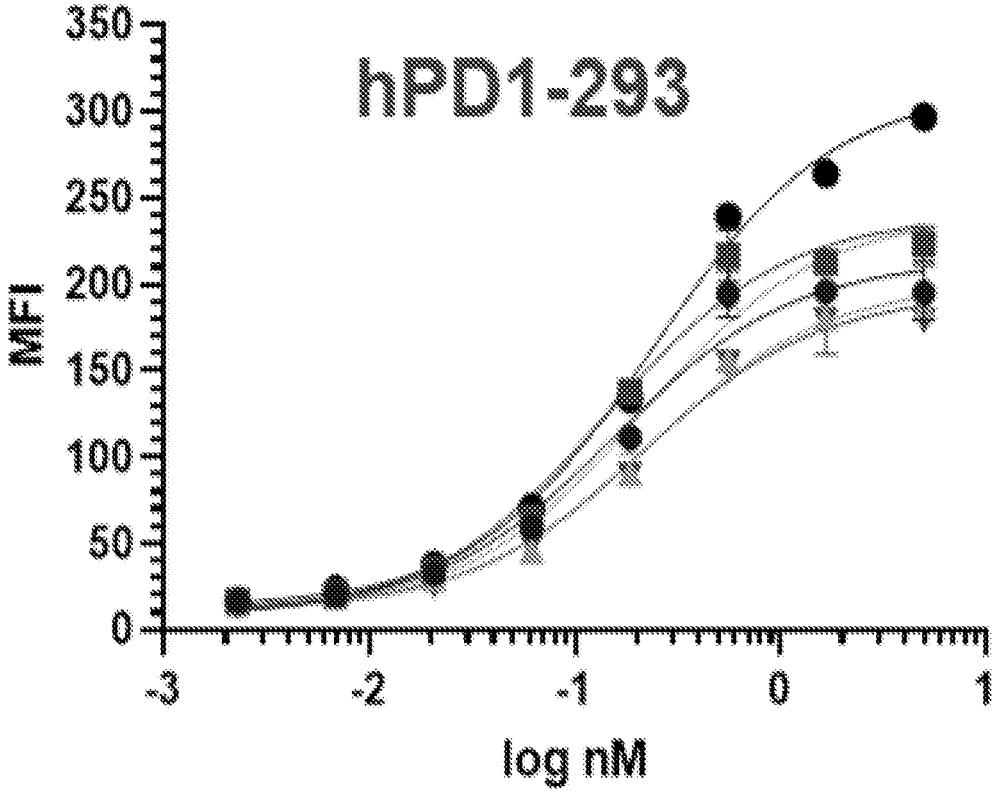


Fig. 13A

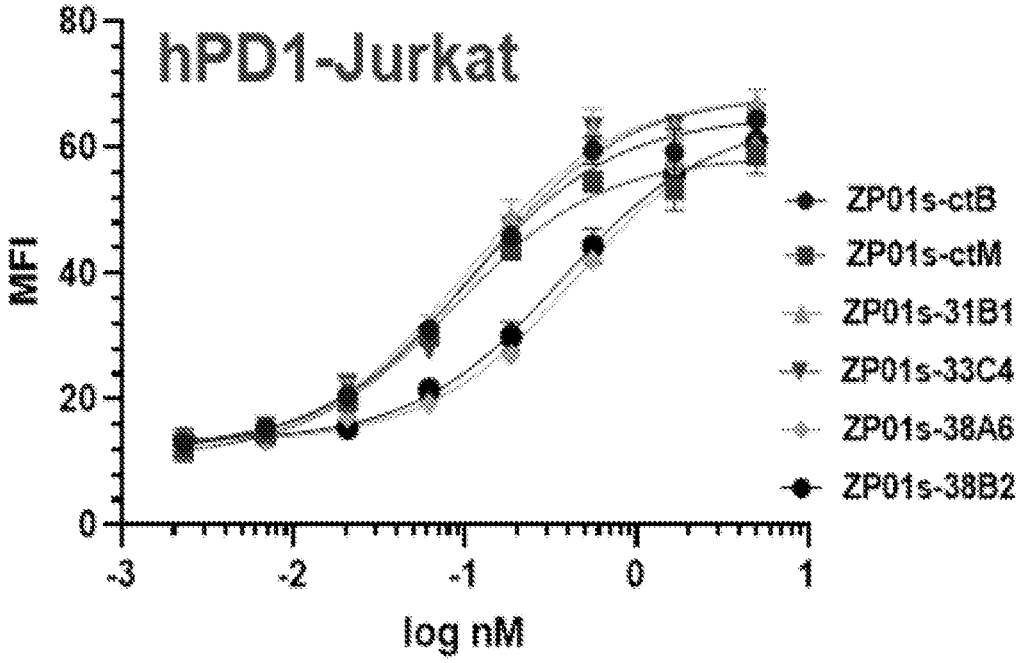


Fig. 13B

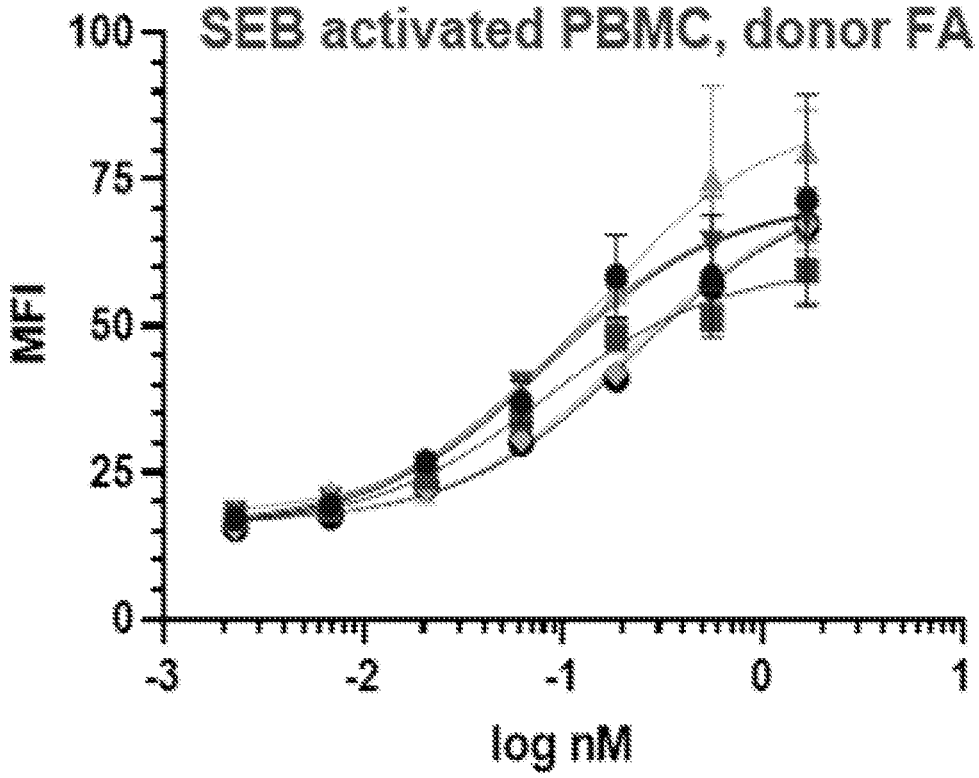


Fig. 13C

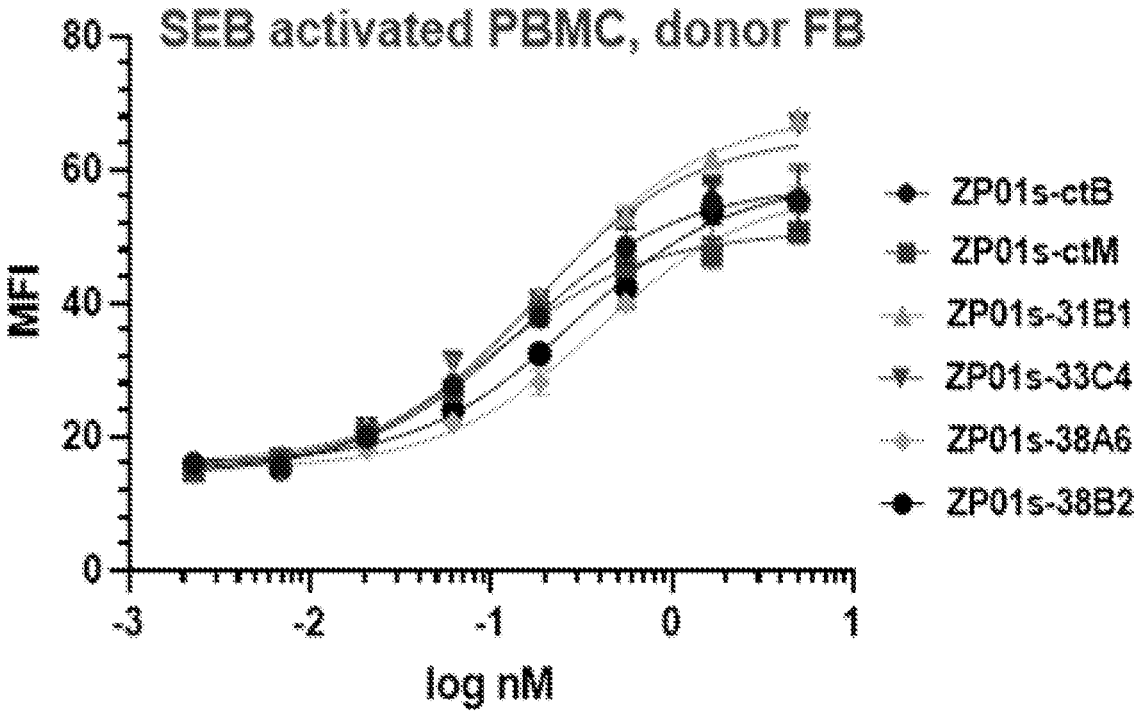


Fig. 13D

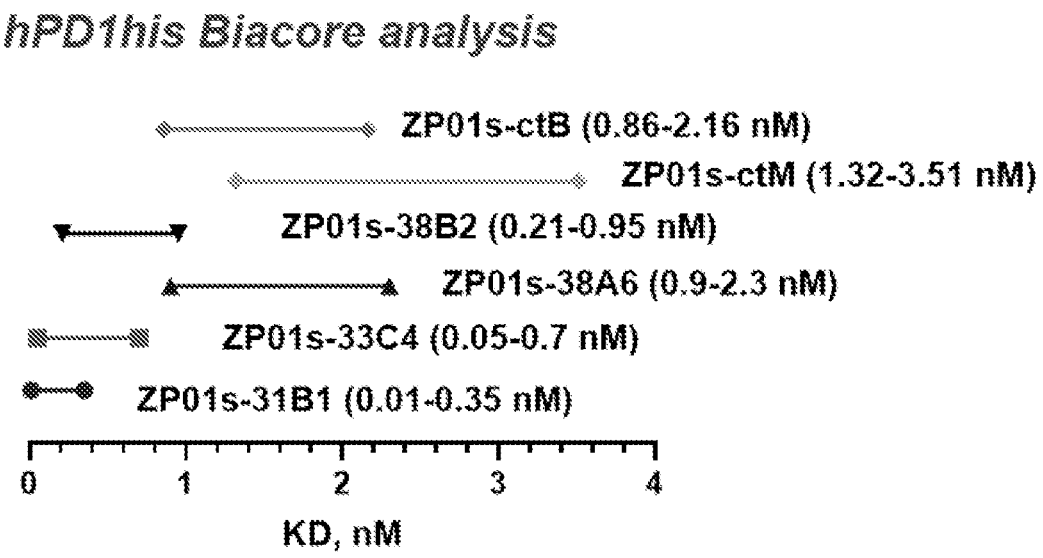


Fig. 14A

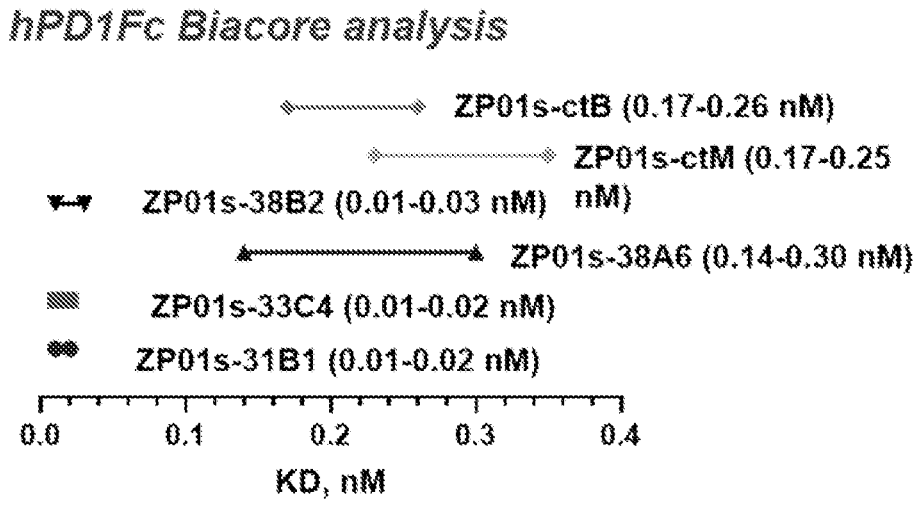


Fig. 14B

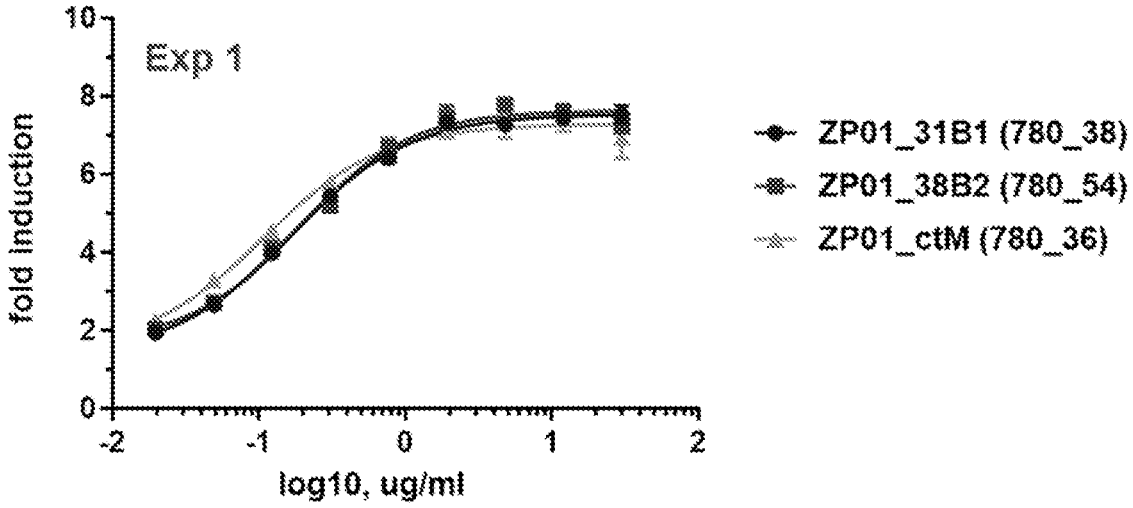


Fig. 15A

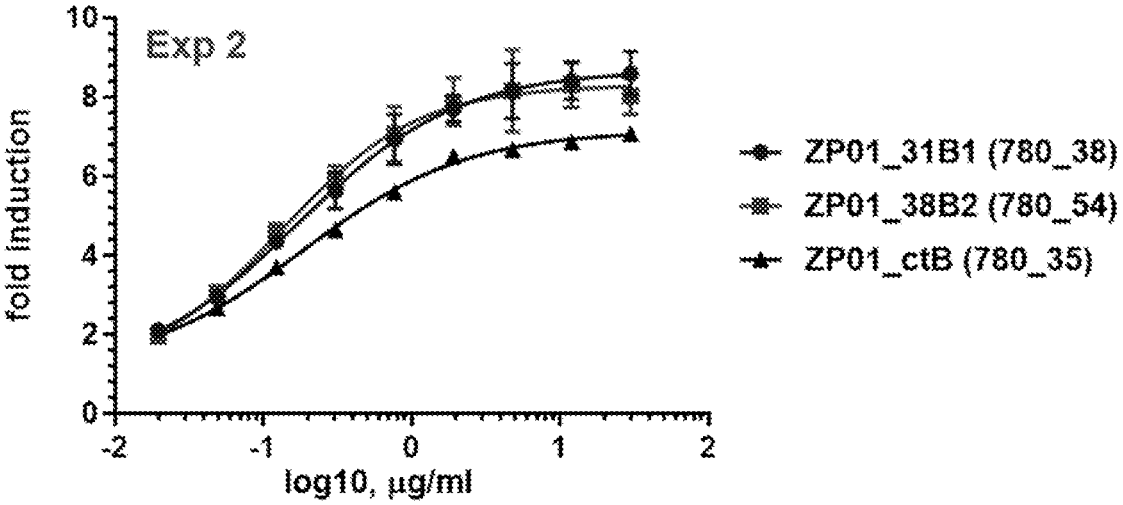


Fig. 15B

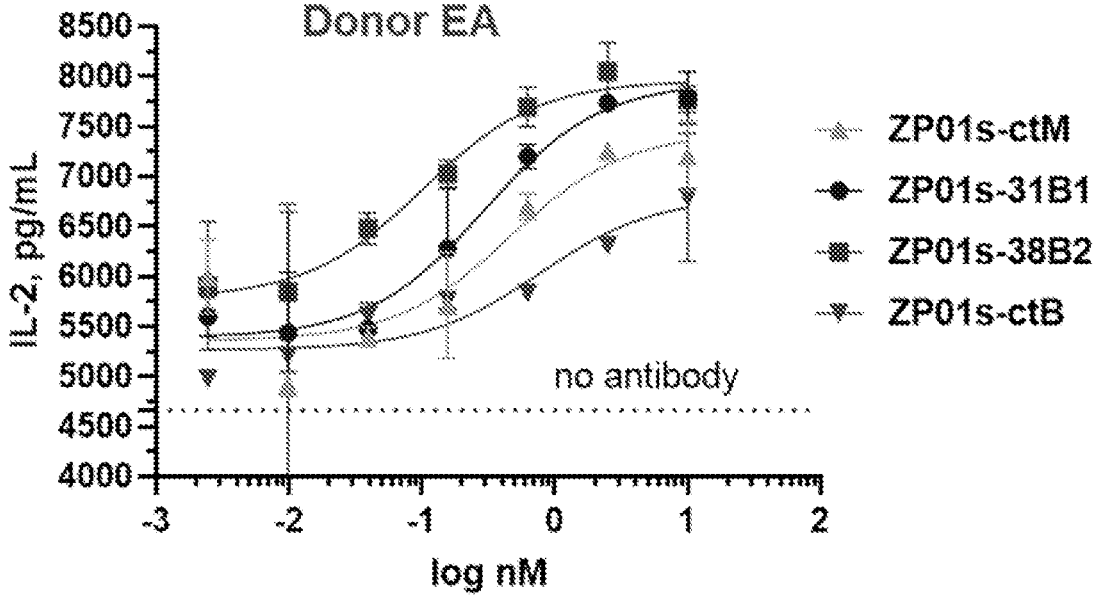


Fig. 16A

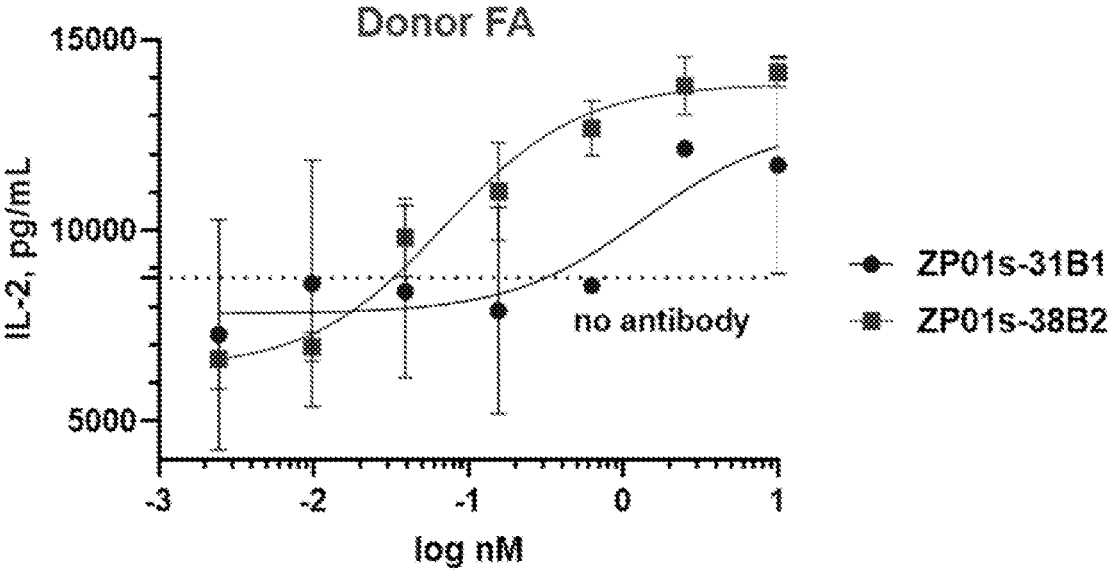


Fig. 16B

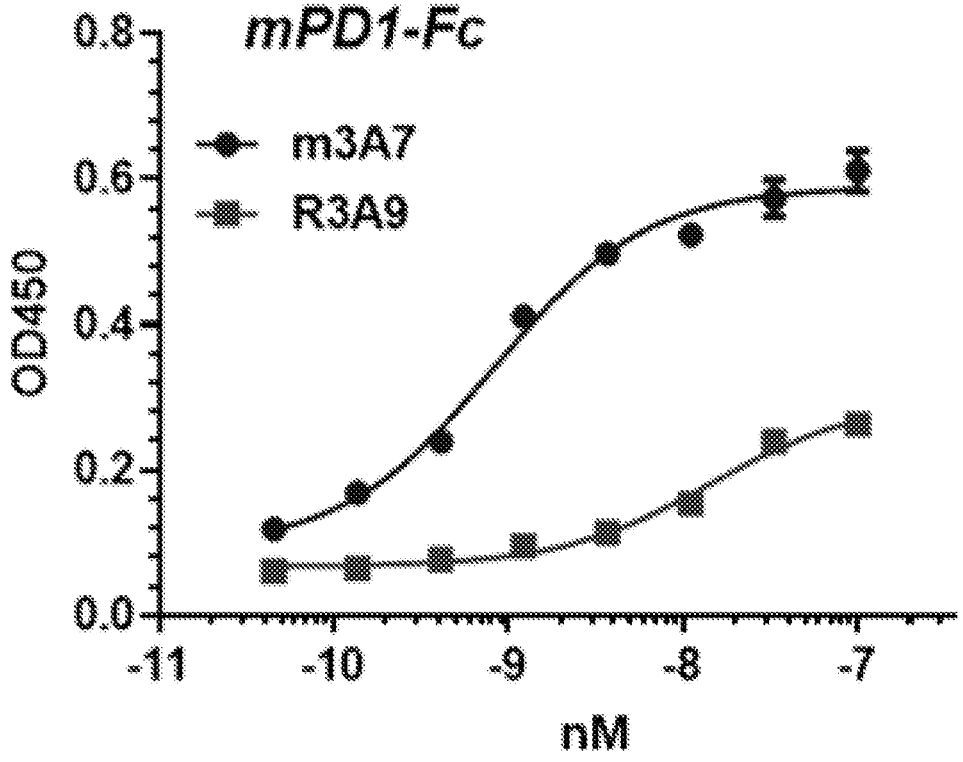


Fig. 17A

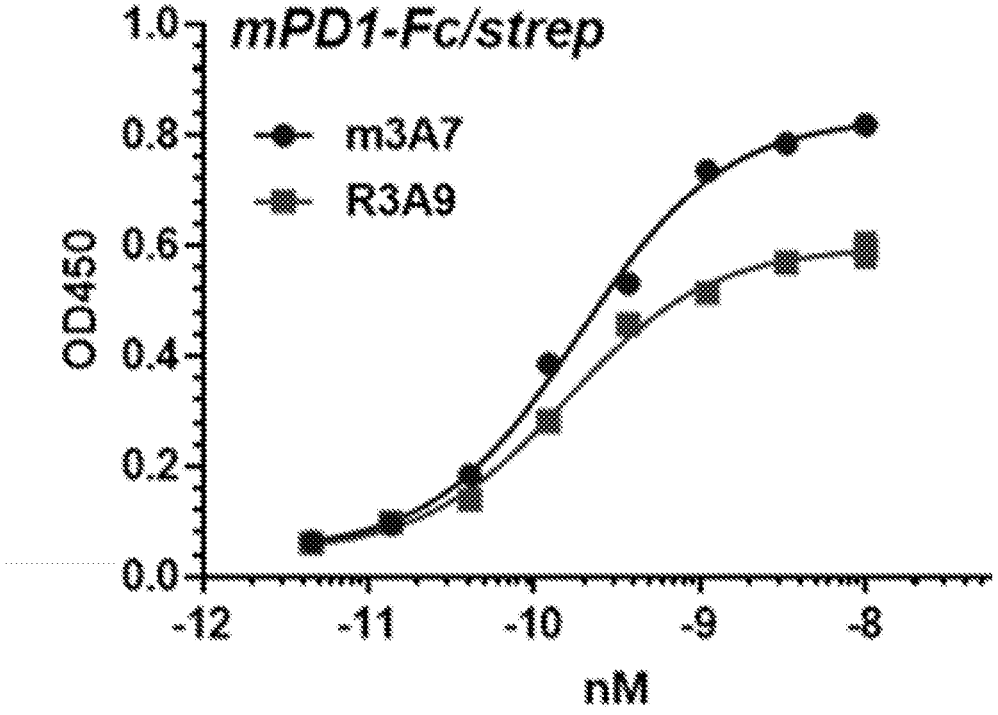


Fig. 17B

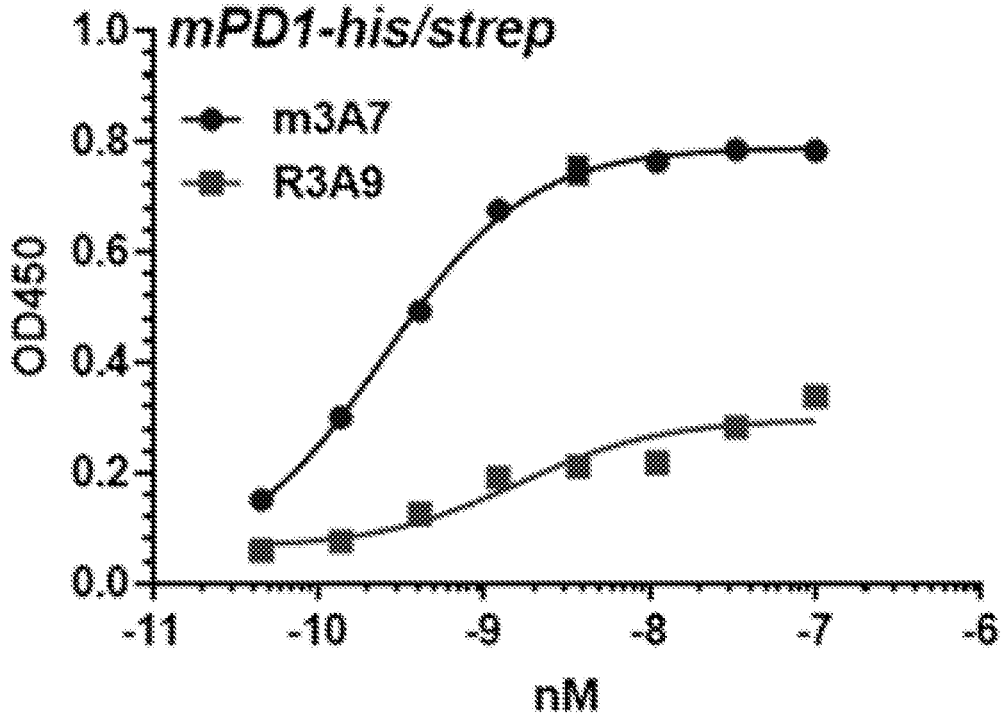


Fig. 17C

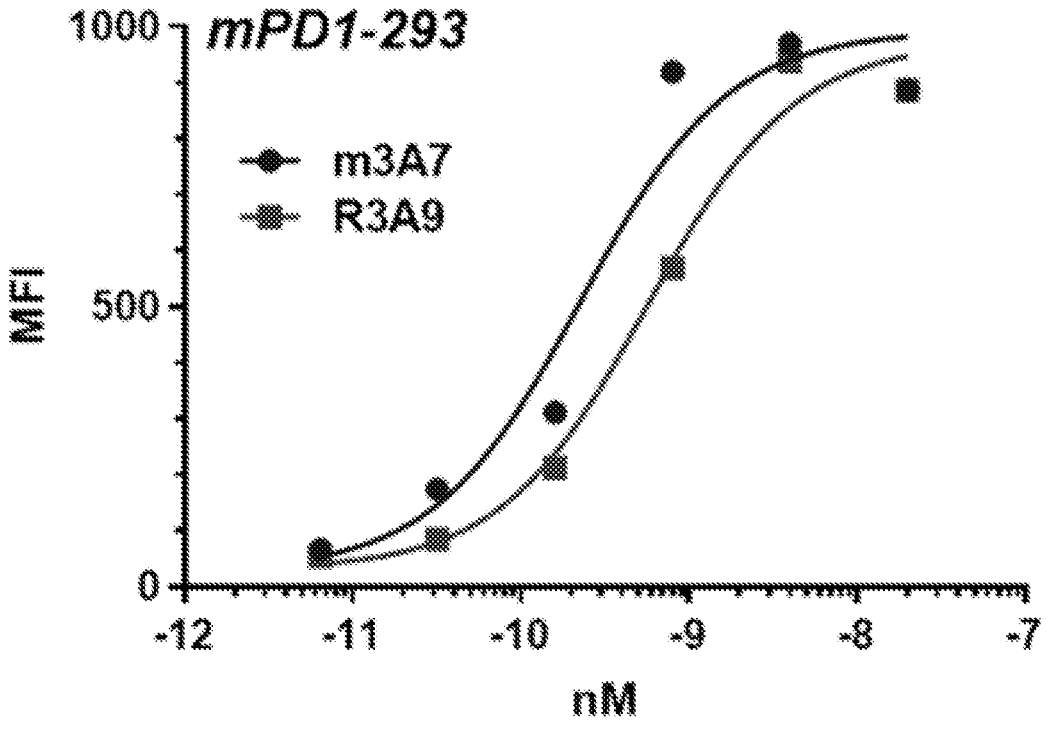


Fig. 17D

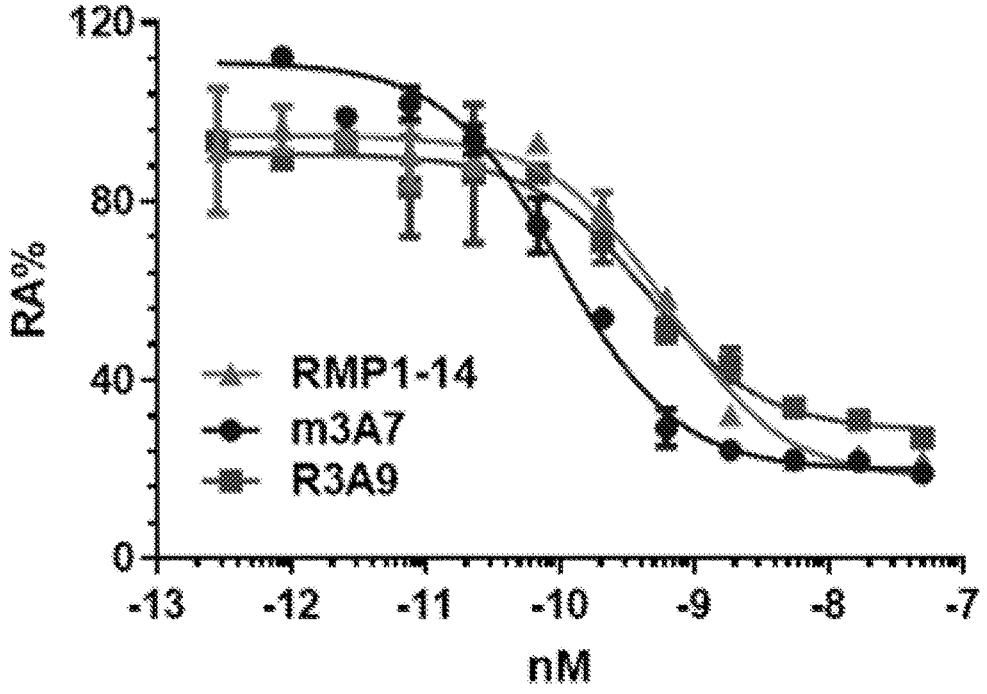


Fig. 17E

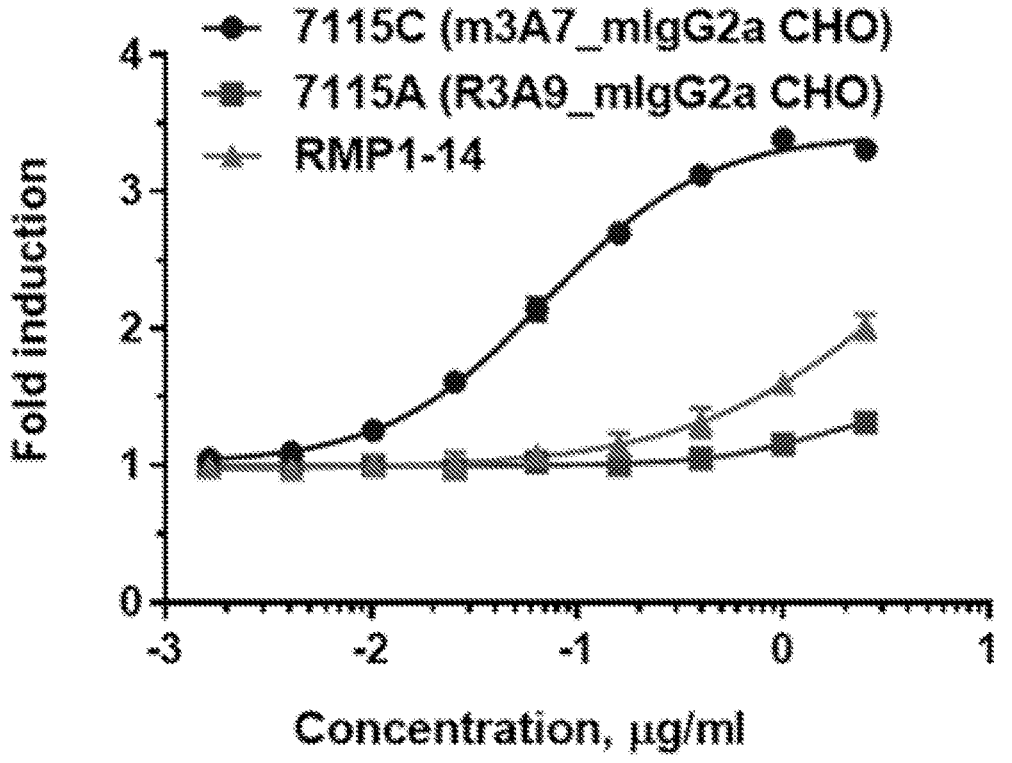


Fig. 17F

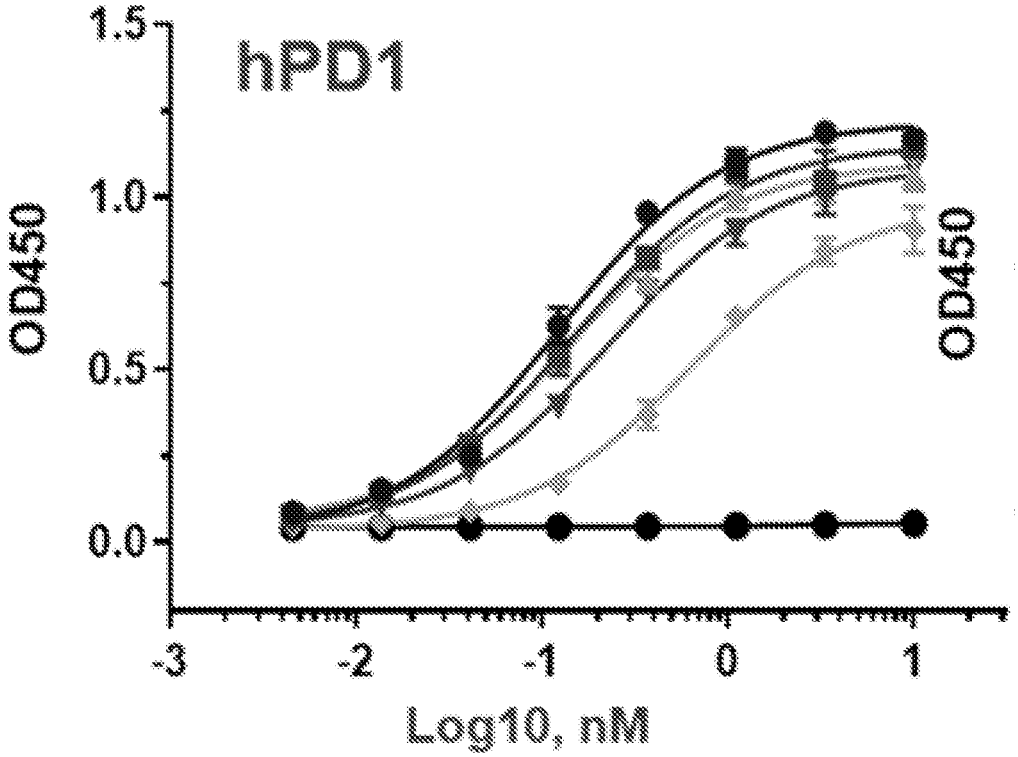


Fig. 18A

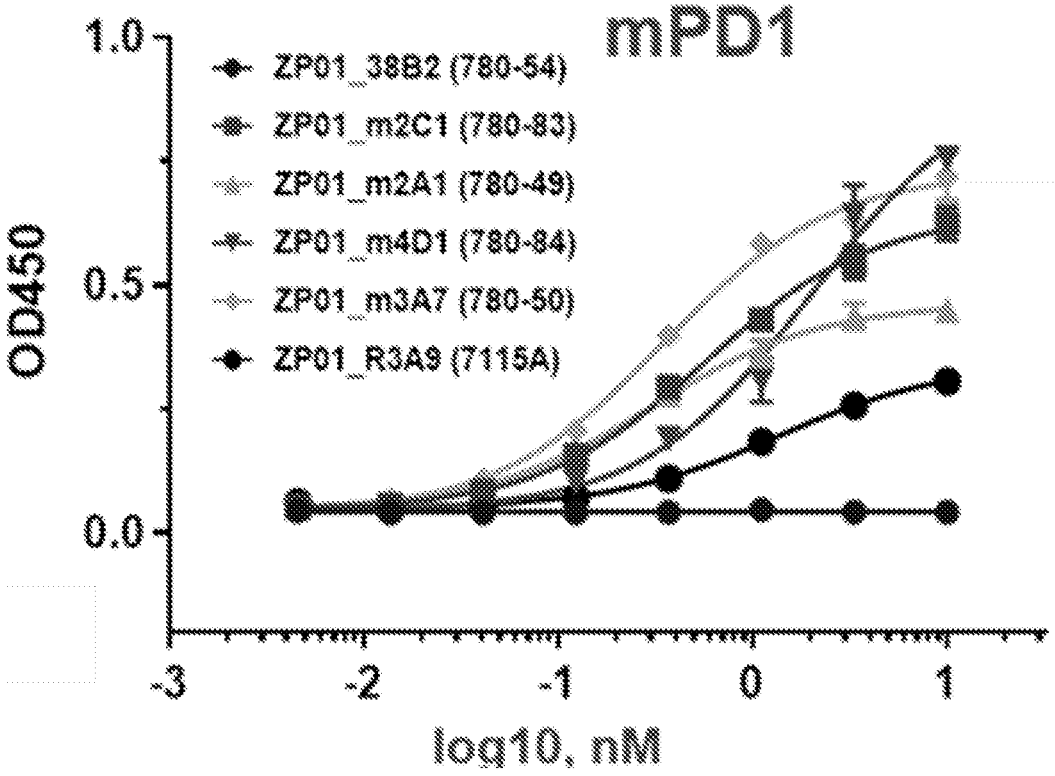


Fig. 18B

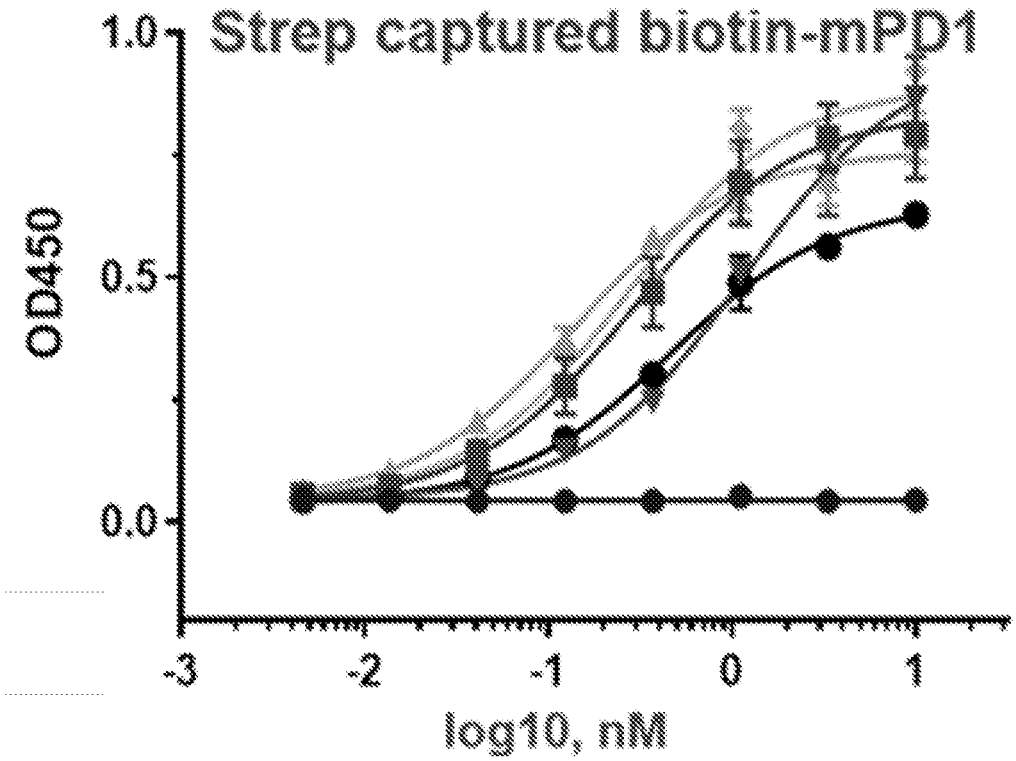


Fig. 18C

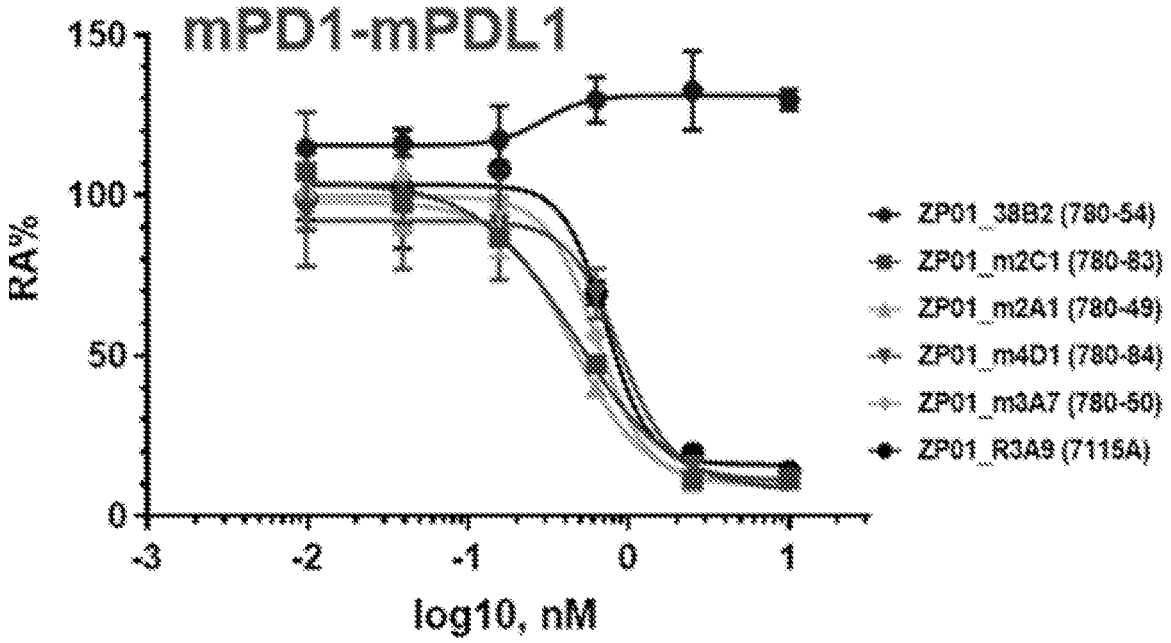


Fig. 18D

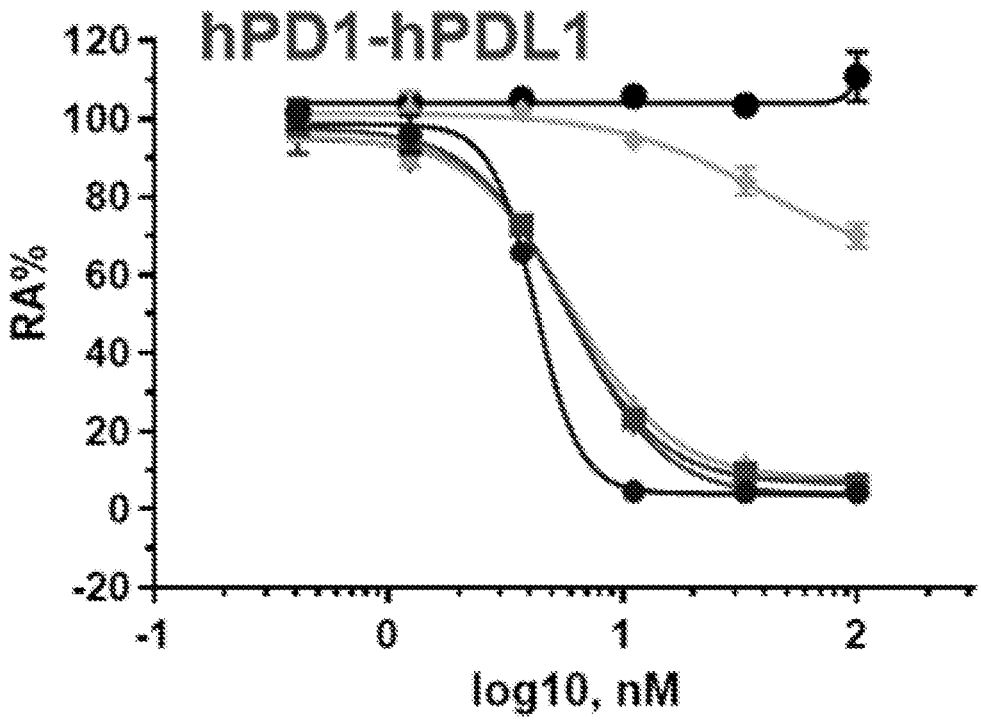


Fig. 18E

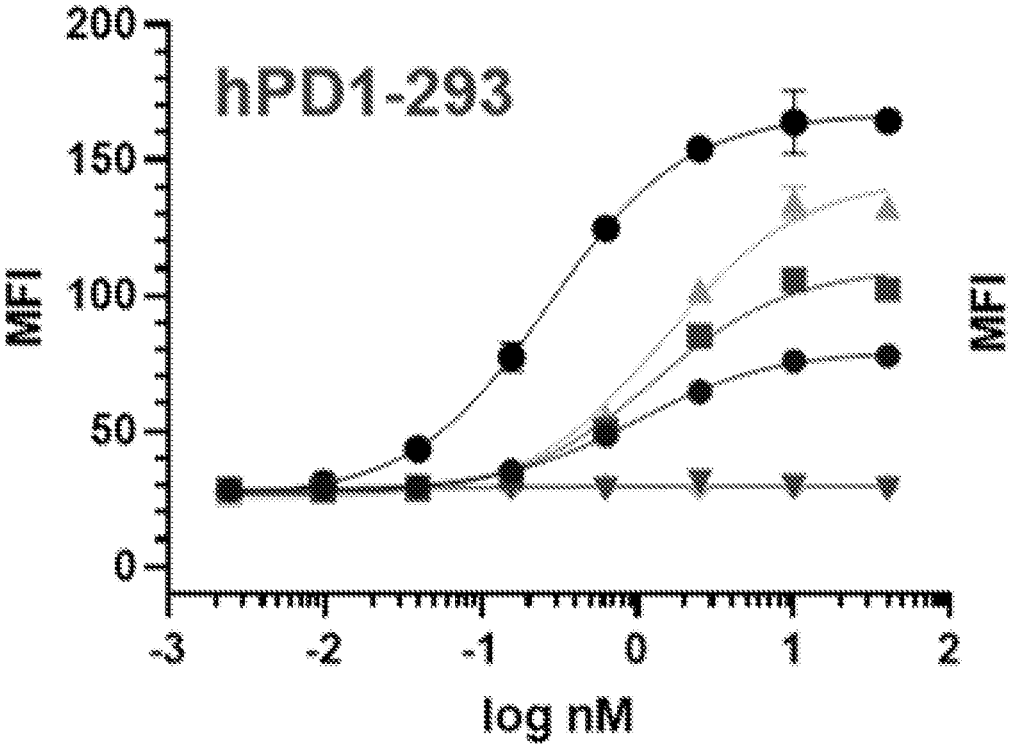


Fig. 19A

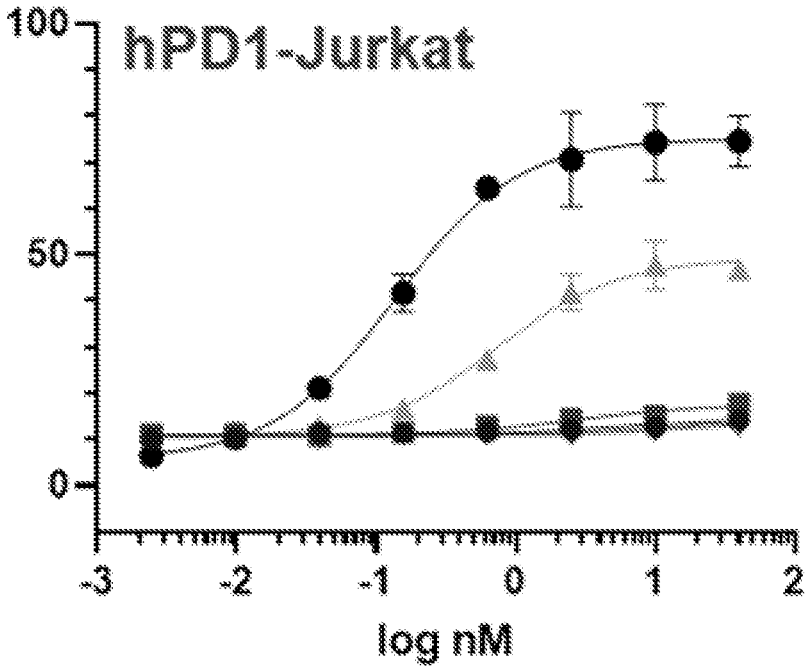


Fig. 19B

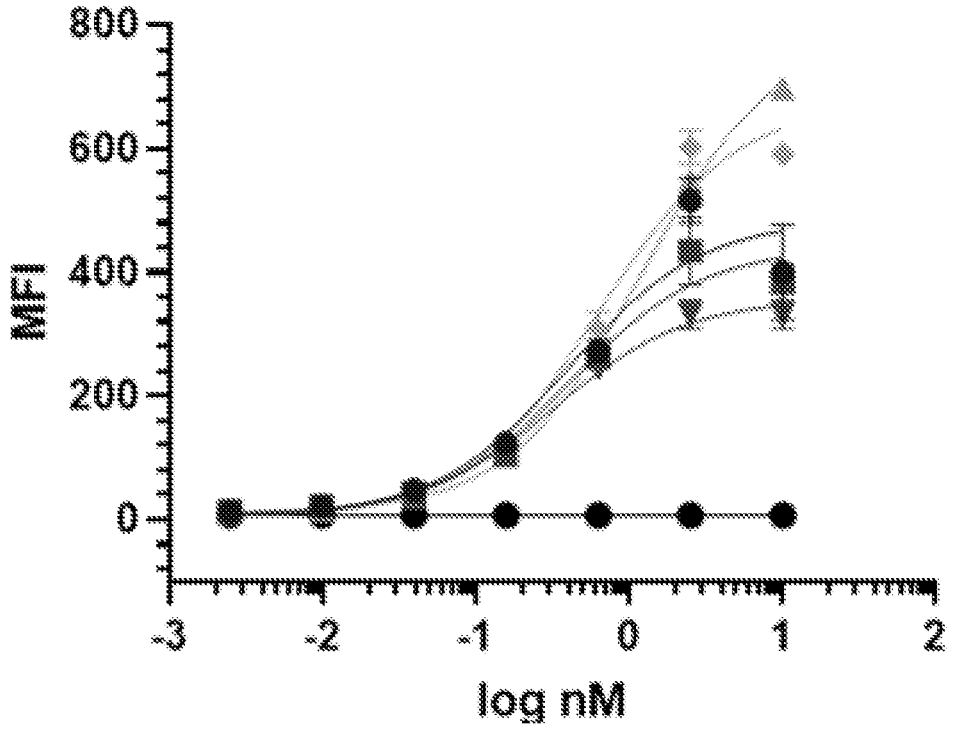


Fig. 19C

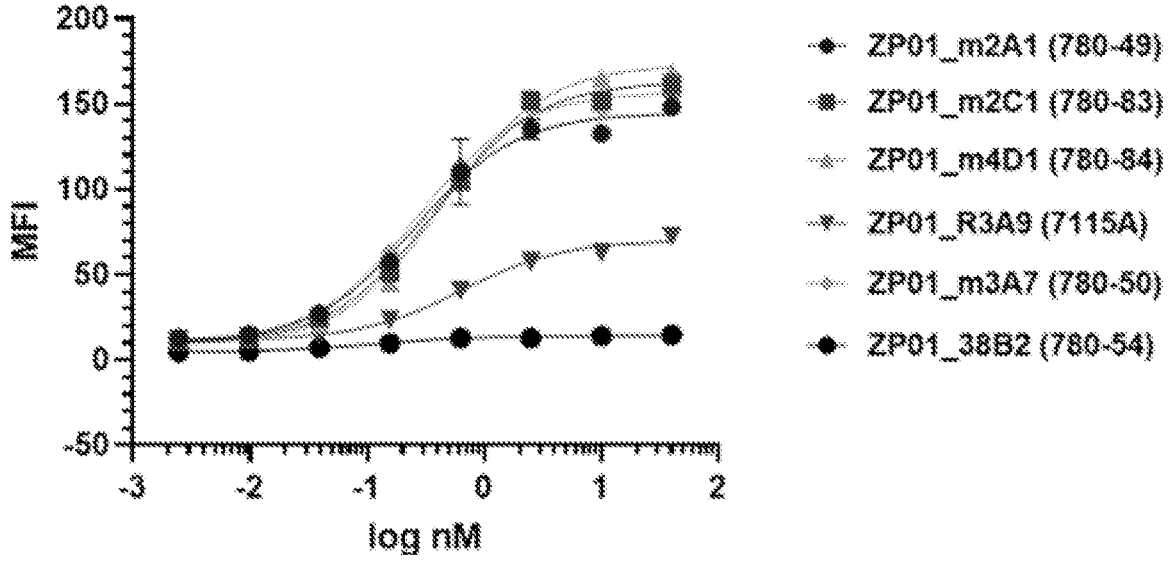


Fig. 19D

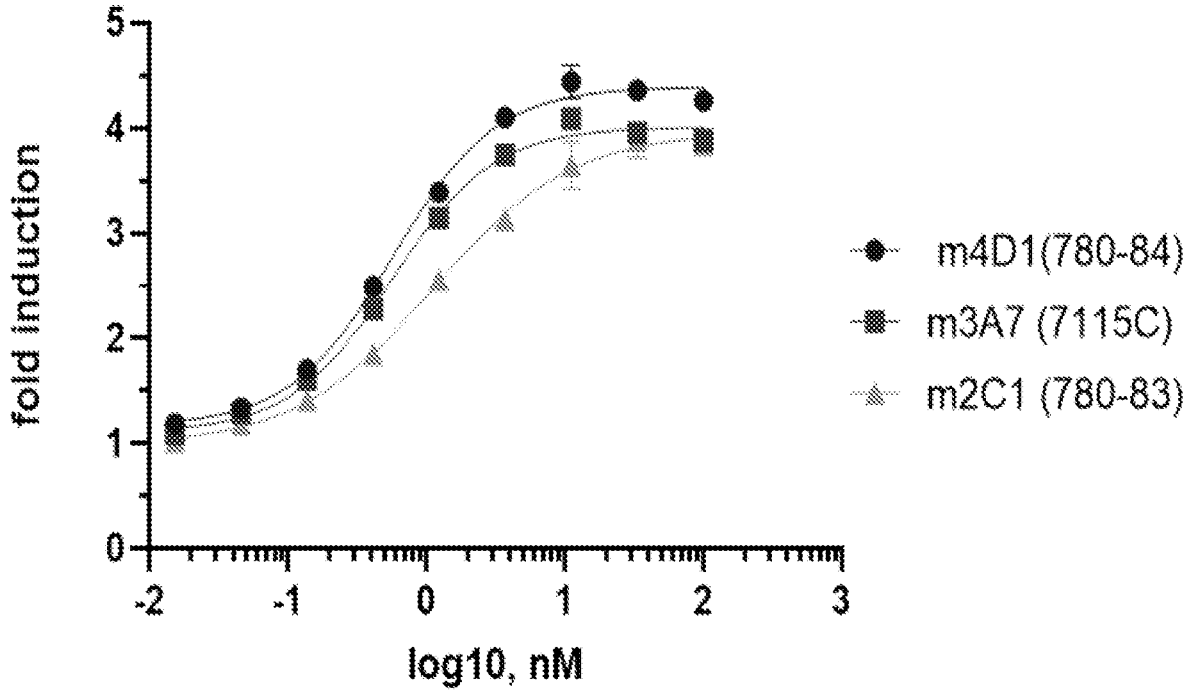


Fig. 20A

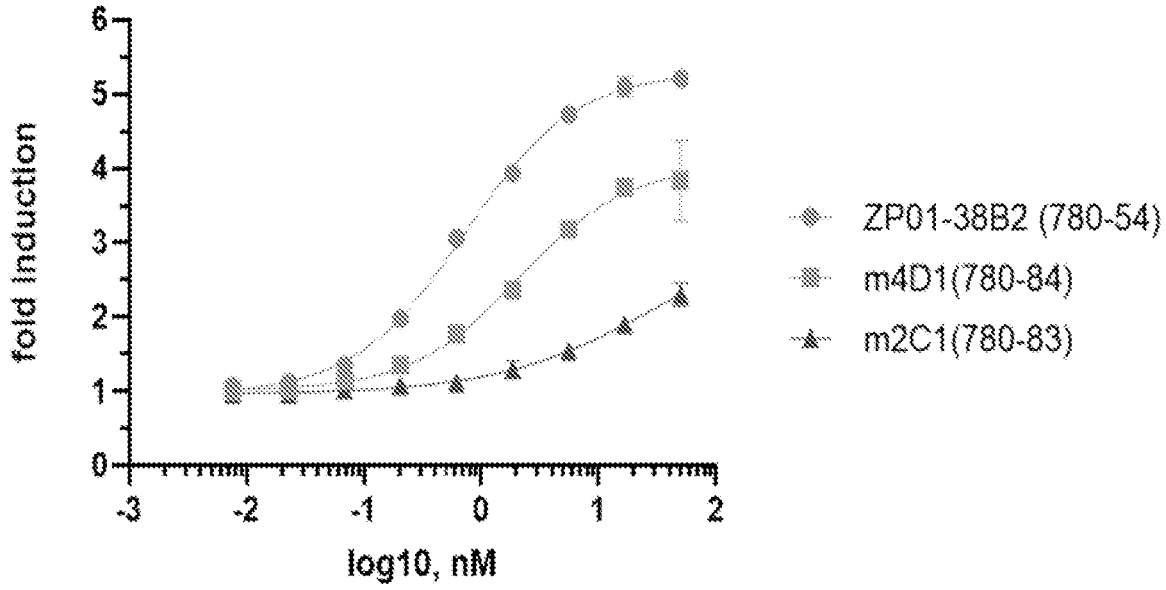
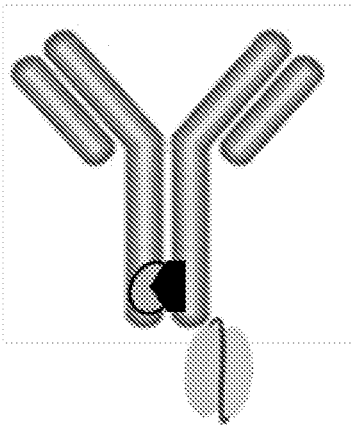
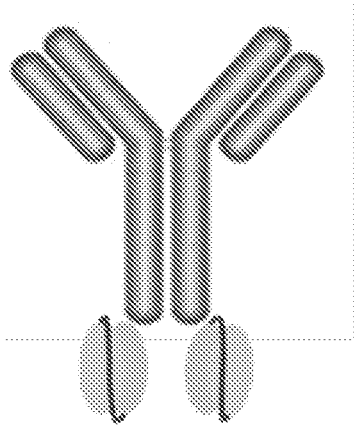


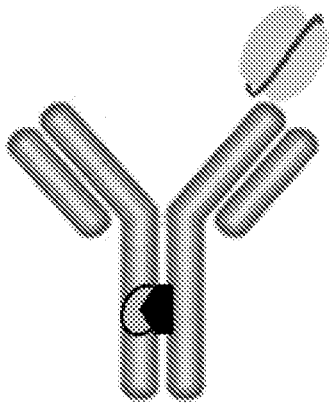
Fig. 20B



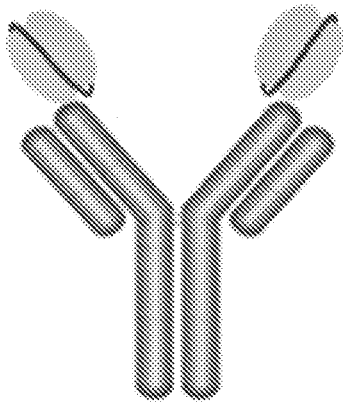
1C-antibody/IL-15



2C-antibody/IL-15

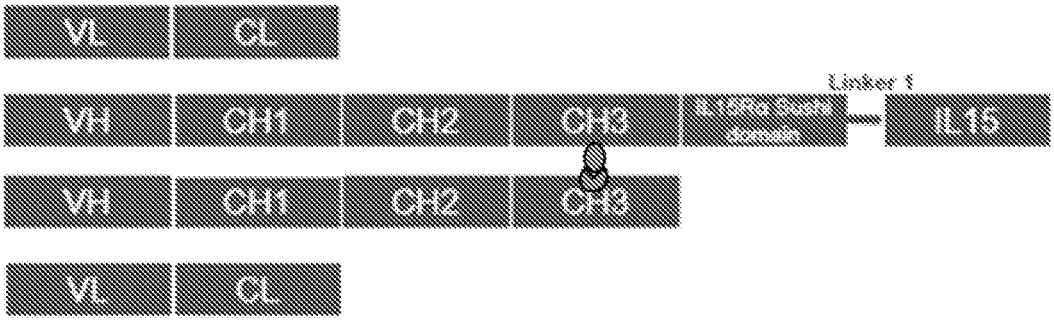


1N-antibody/IL-15

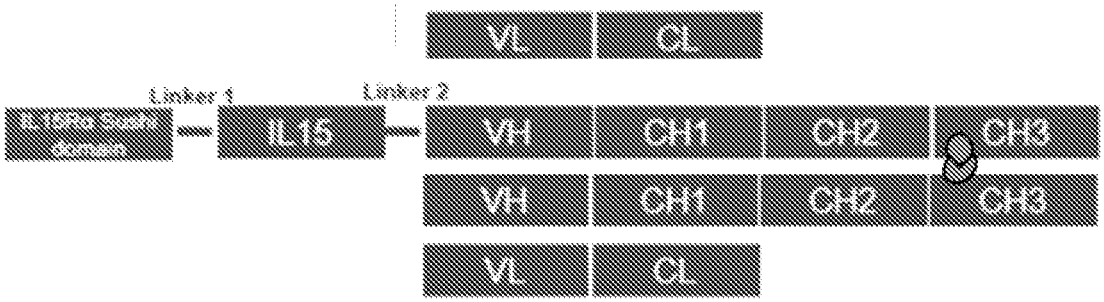


2N-antibody/IL-15

Fig. 21A



1C-antibody/IL-15



1N-antibody/IL-15

Fig. 21B

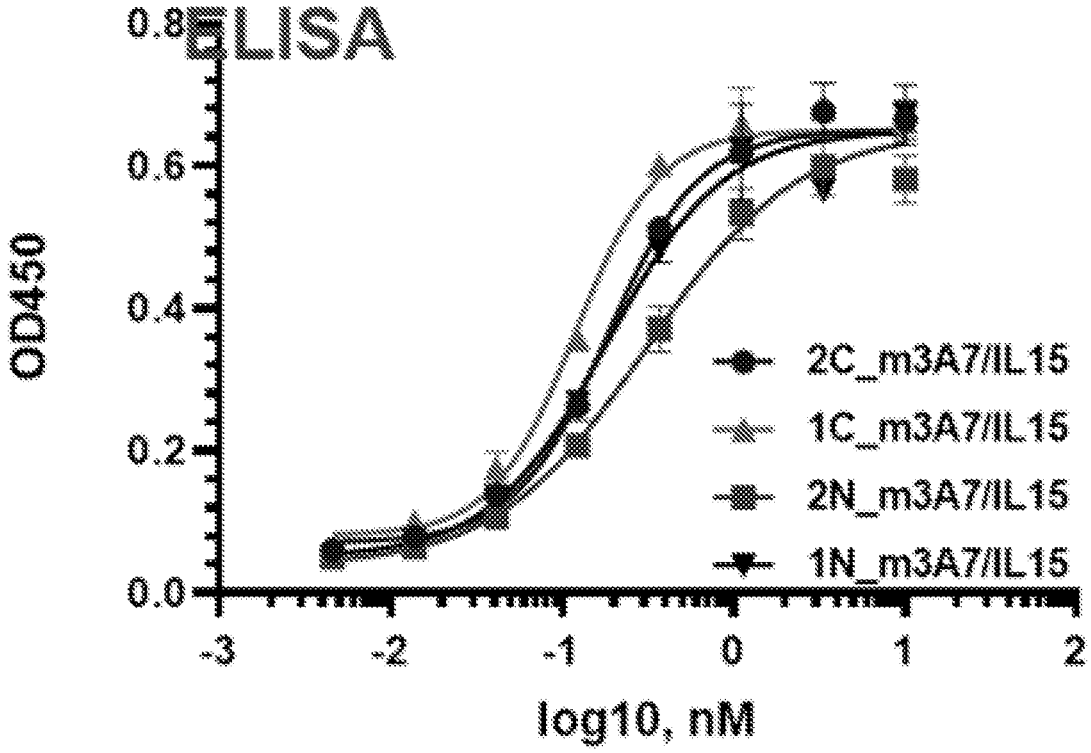


Fig. 22A

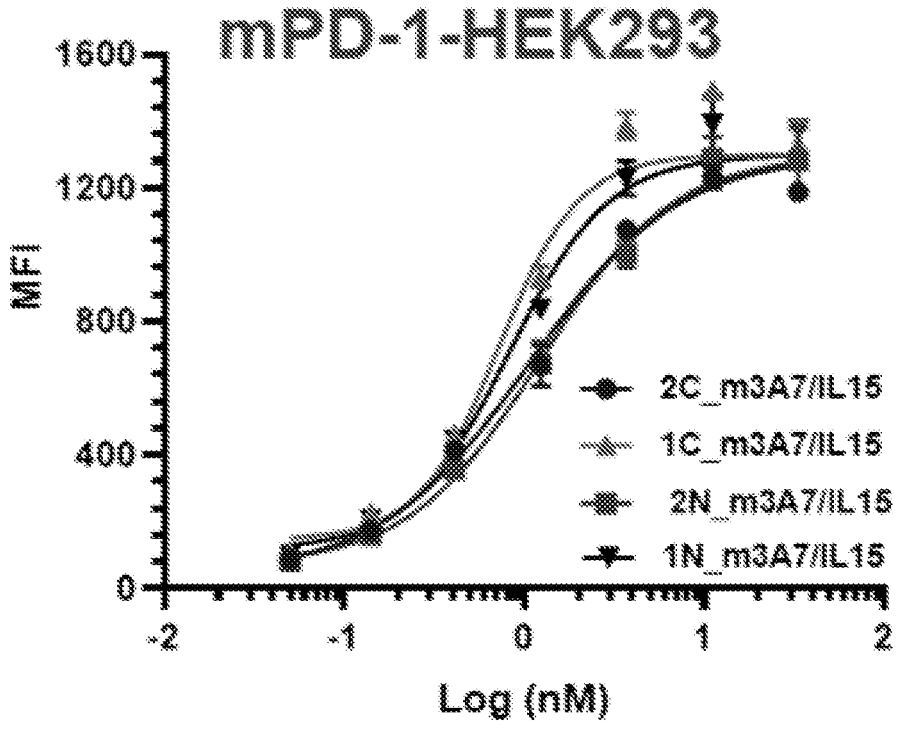


Fig. 22B

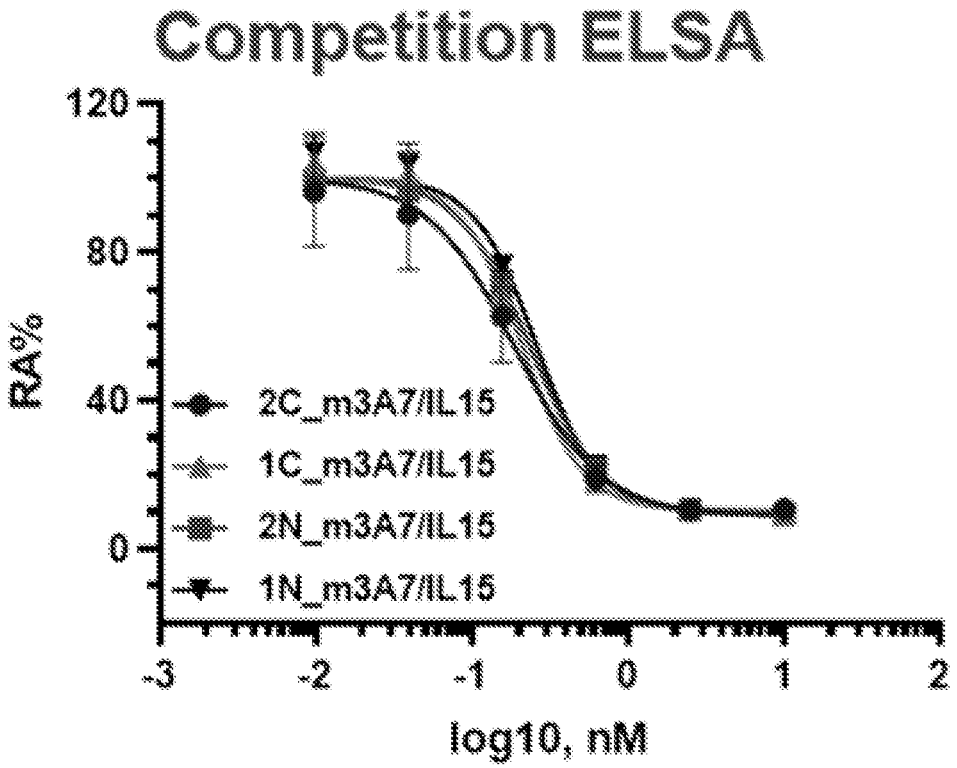


Fig. 22C

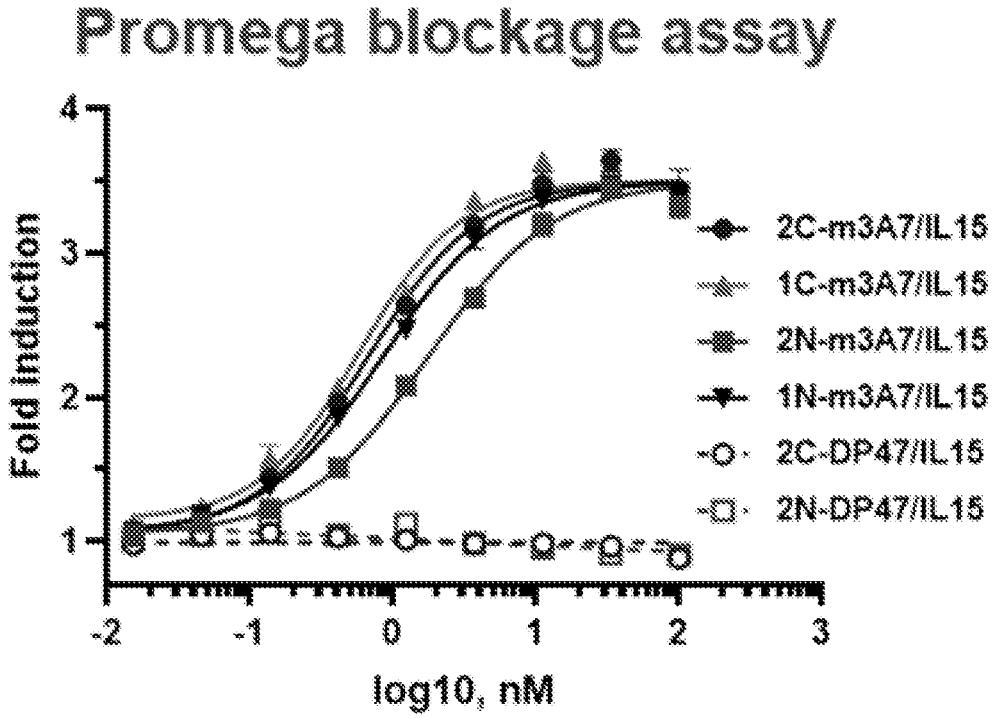


Fig. 22D

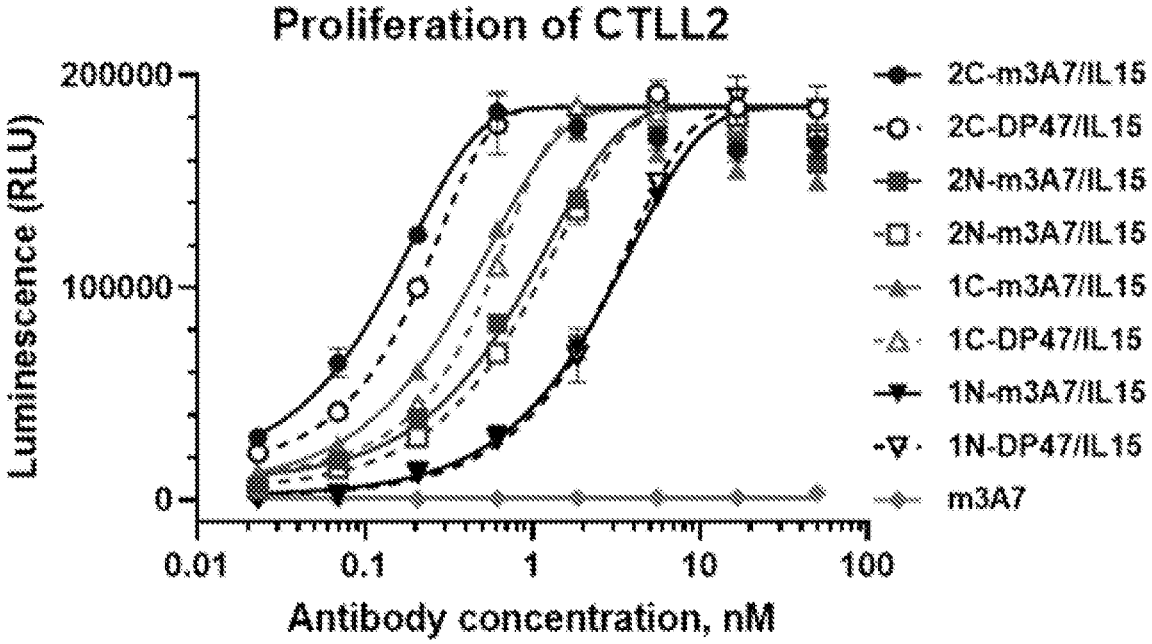


Fig. 23A

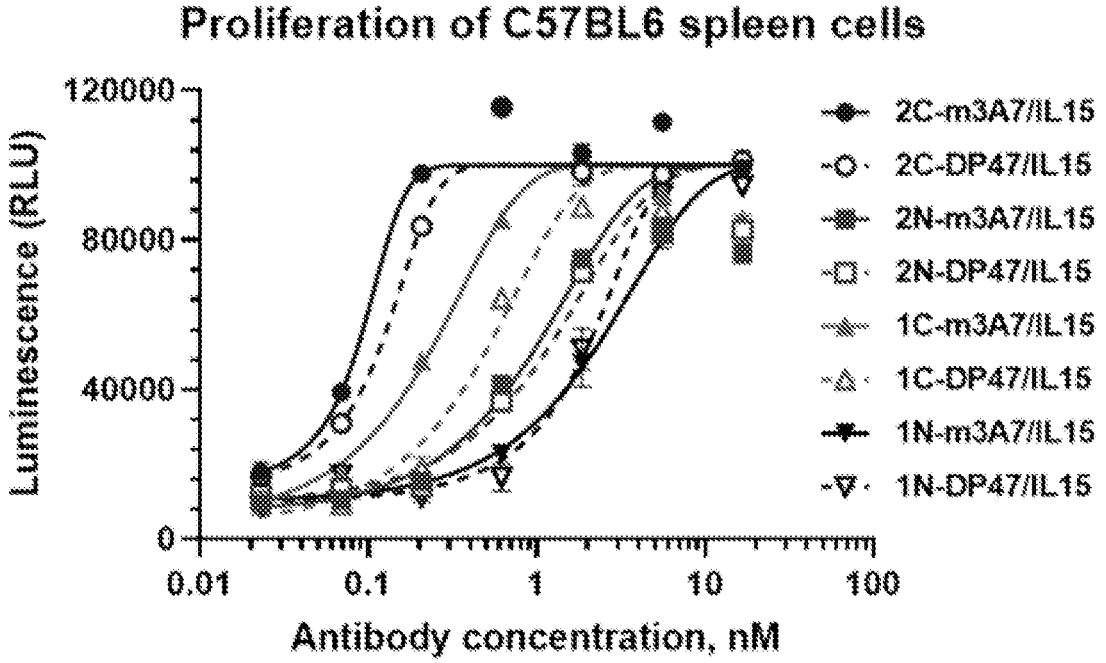


Fig. 23B

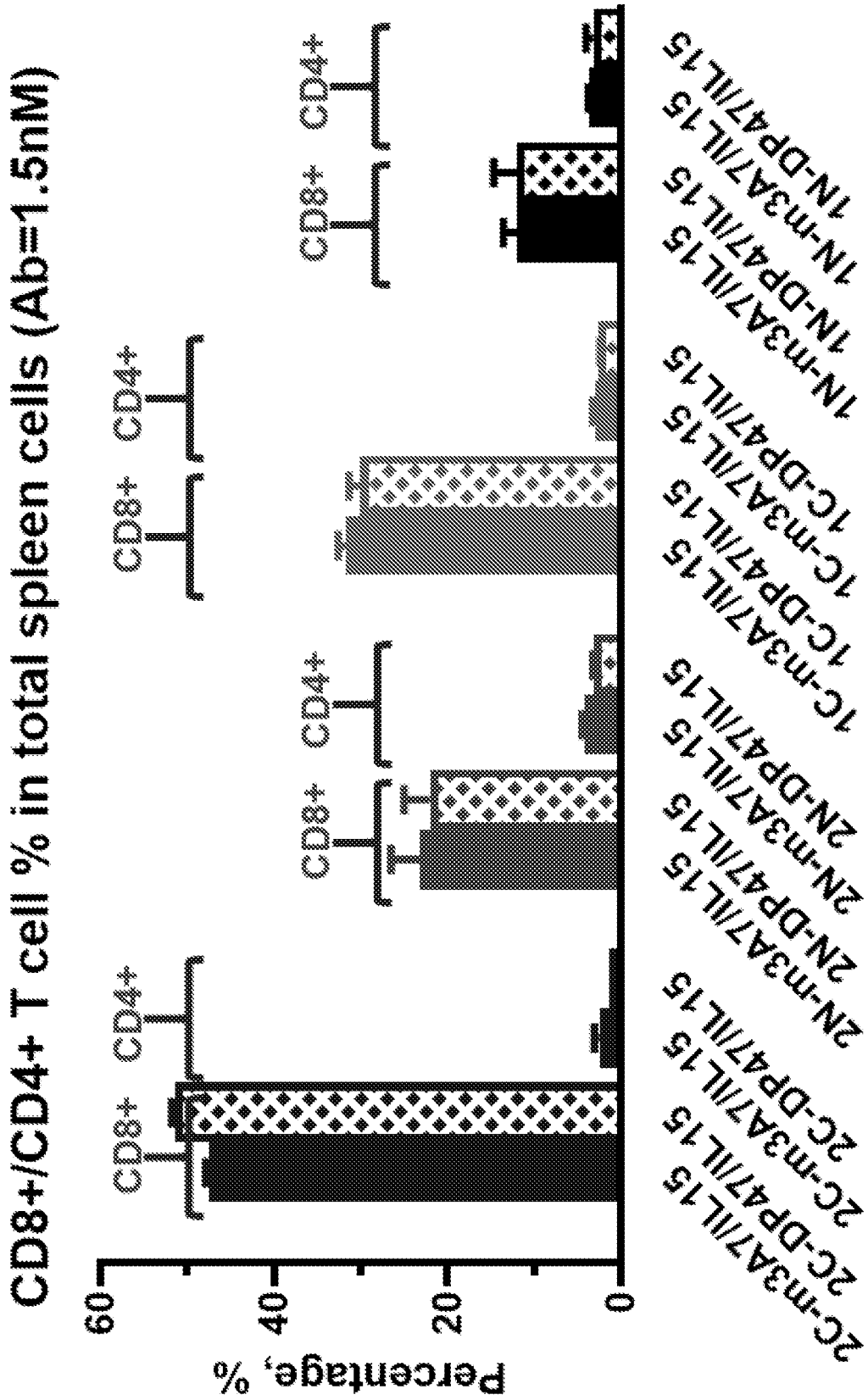

CD8+/CD4+ T cell % in total spleen cells (Ab=1.5nM)
Percentage, %
60
40
20
0
CD8+ CD4+
2C-m3A7/IL-15
2C-DP47/IL-15
2N-m3A7/IL-15
2N-DP47/IL-15
1C-m3A7/IL-15
1C-DP47/IL-15
1N-m3A7/IL-15
1N-DP47/IL-15

Fig. 23C

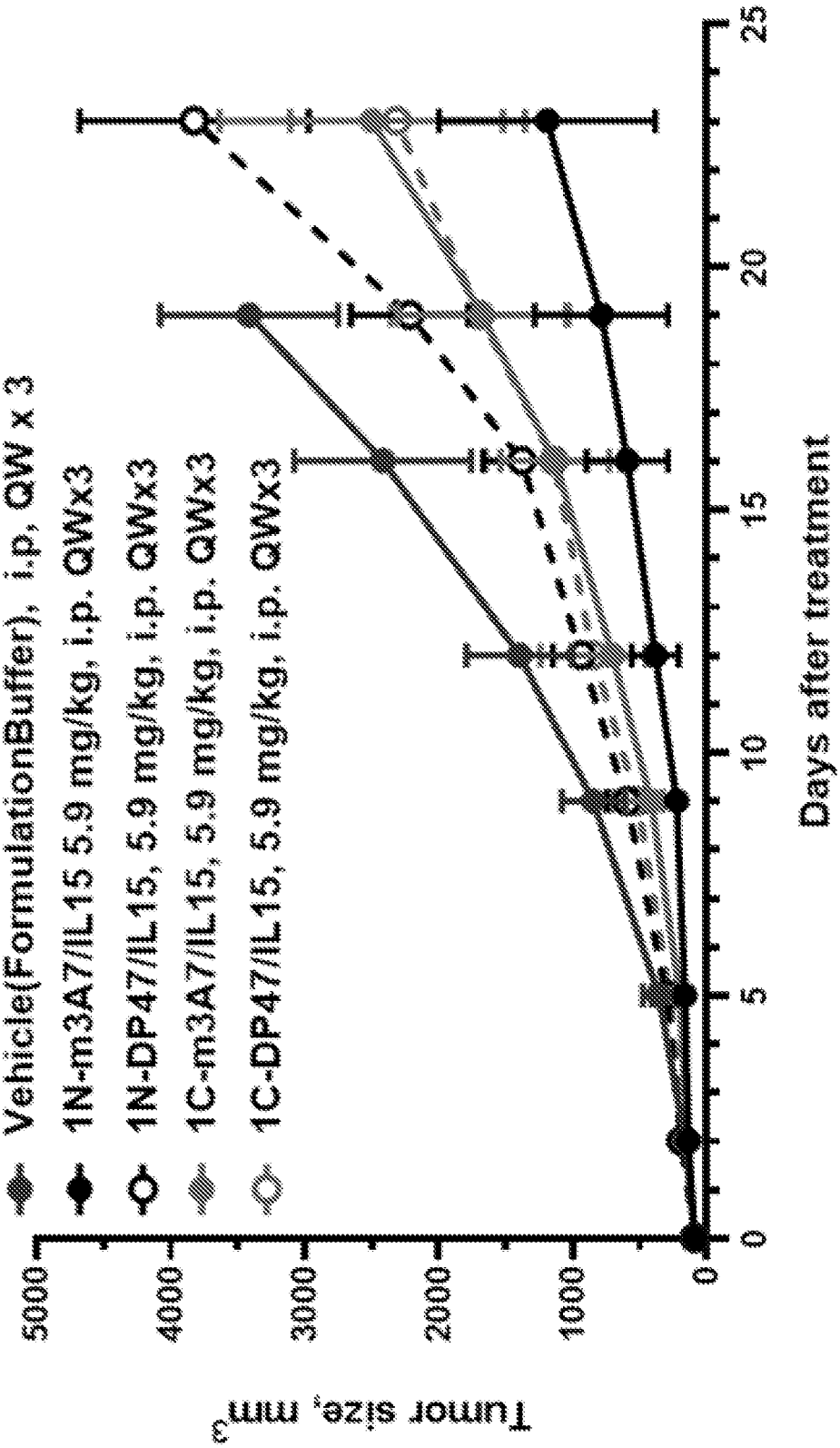

Vehicle(FormulationBuffer), i.p, QW x 3
1N-m3A7/IL15 5.9 mg/kg, i.p. QWx3
1N-DP47/IL15, 5.9 mg/kg, i.p. QWx3
1C-m3A7/IL15, 5.9 mg/kg, i.p. QWx3
1C-DP47/IL15, 5.9 mg/kg, i.p. QWx3
Tumor size, mm3
5000
4000
3000
2000
1000
0
0
5
10
15
20
25
Days after treatment

Fig. 24

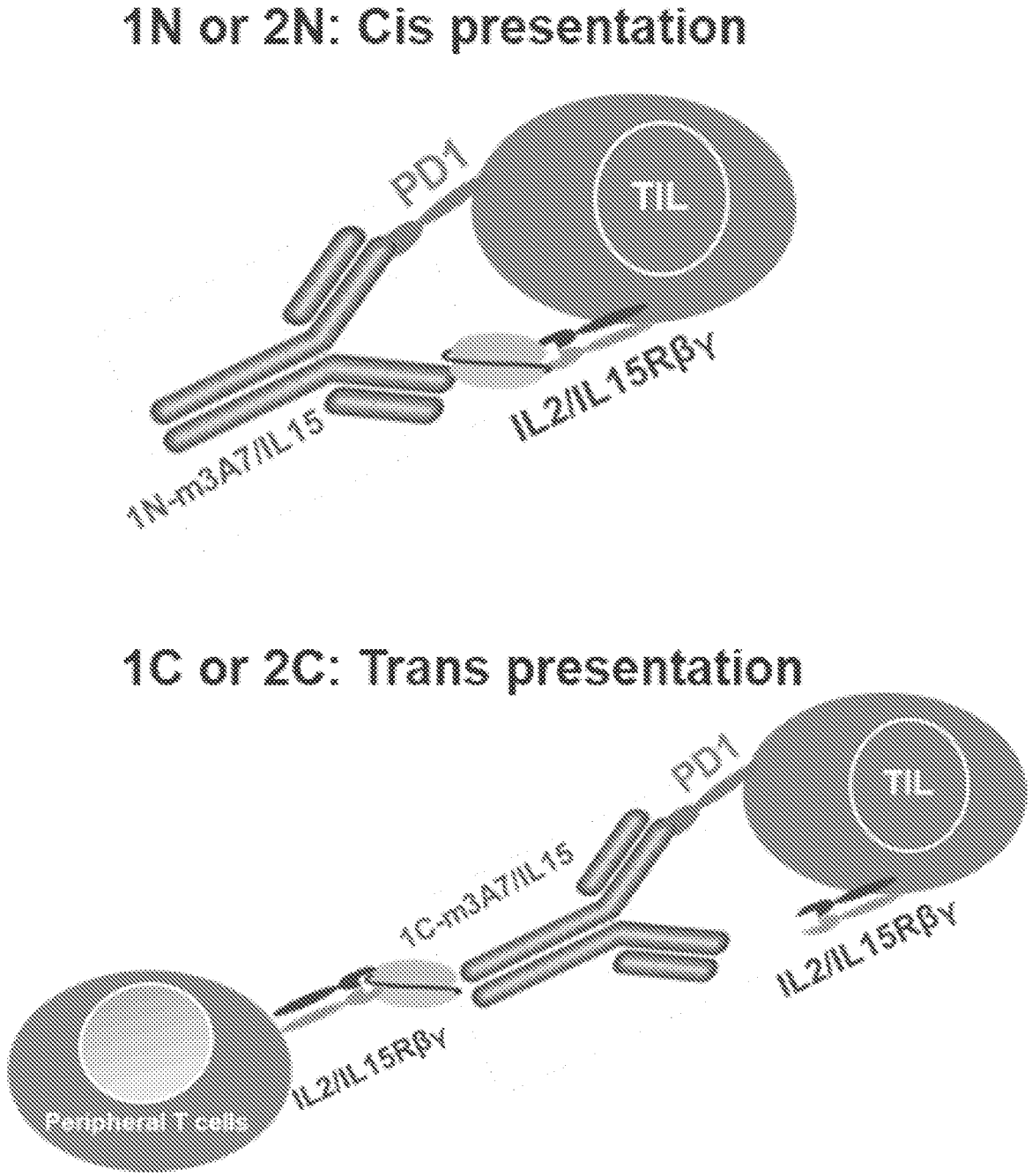

1N or 2N: Cis presentation
PD1
TIL
1N-m3A7/IL15
IL2/IL15Rβγ
1C or 2C: Trans presentation
PD1
TIL
1C-m3A7/IL15
IL2/IL15Rβγ
IL2/IL15Rβγ
Peripheral T cells

Fig. 25A

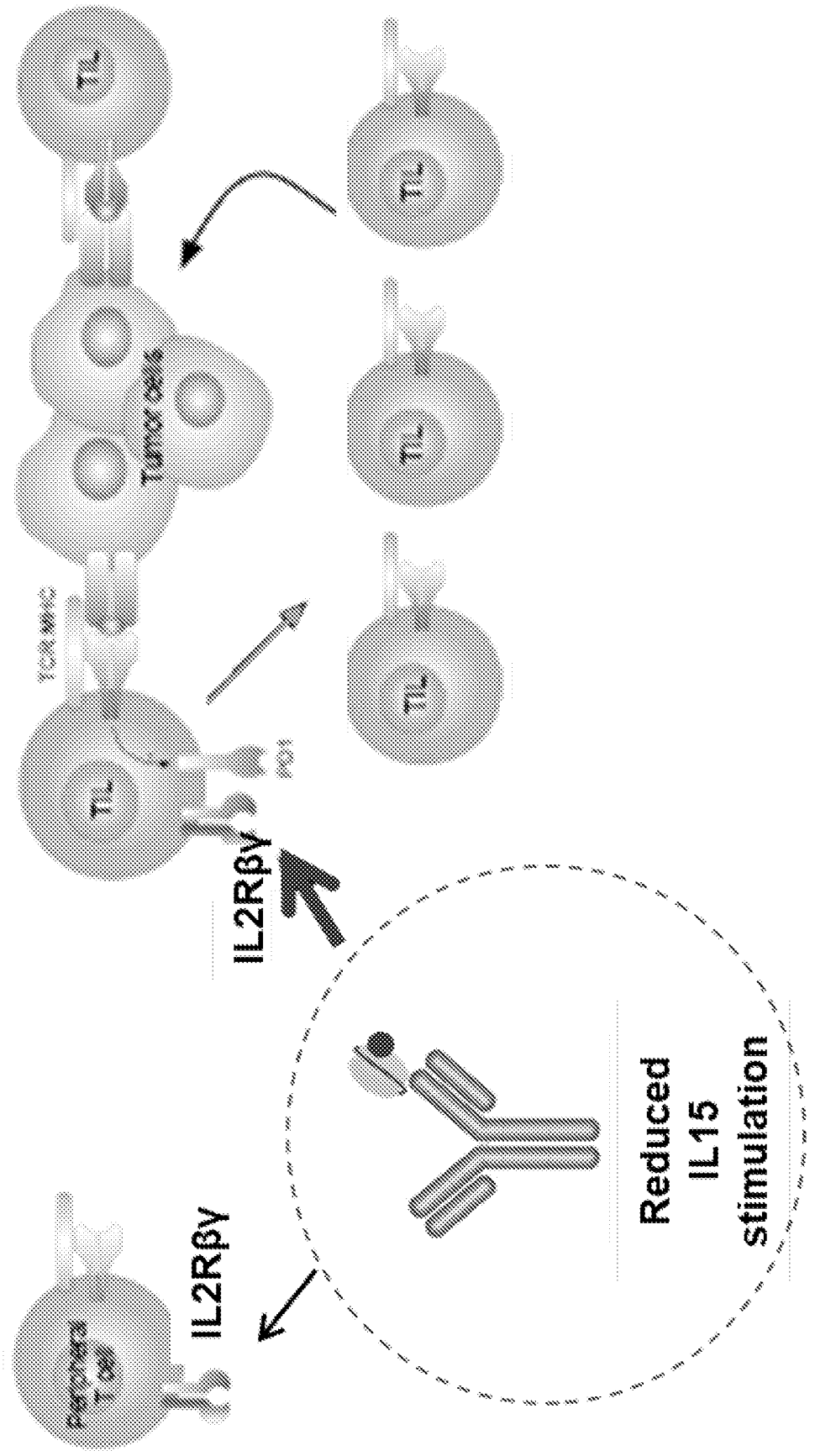

TIL
TIL
TIL
TIL
TIL
Tumor cells
TCR MHC
PD1
IL2Rβγ
Reduced
IL15
stimulation
IL2Rβγ

Fig. 25B

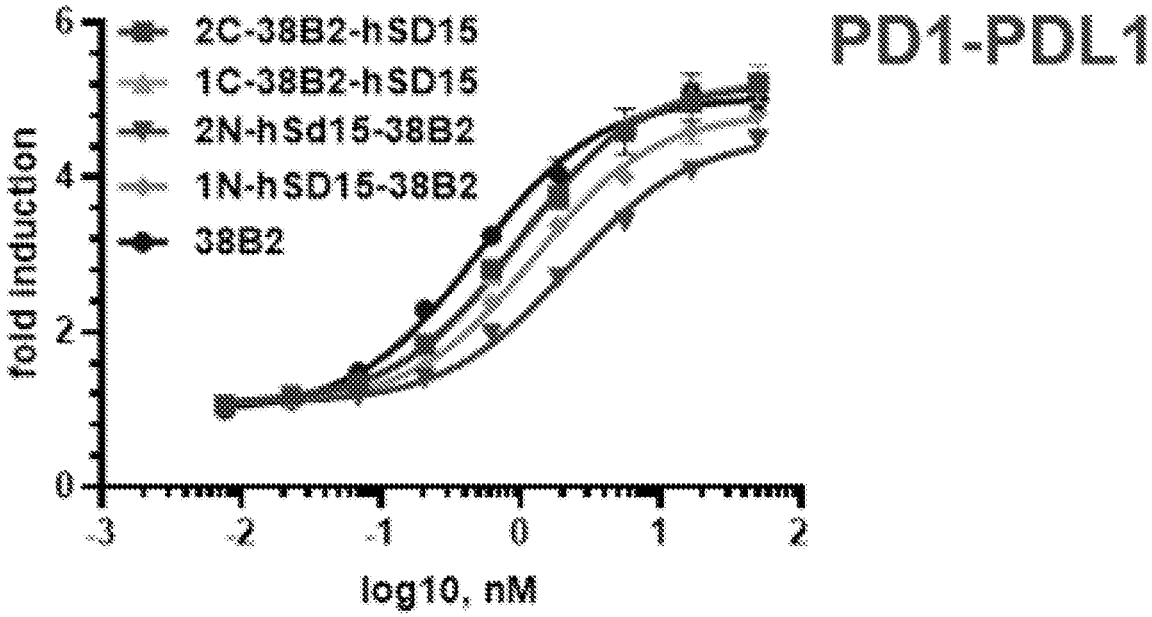


Fig. 26A

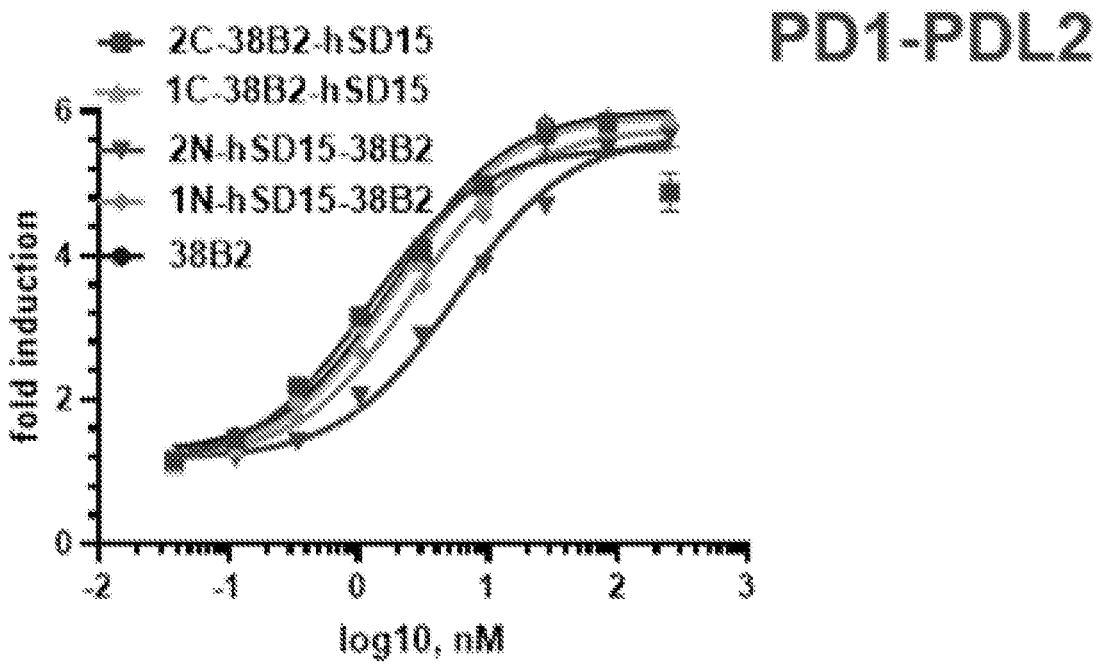


Fig. 26B

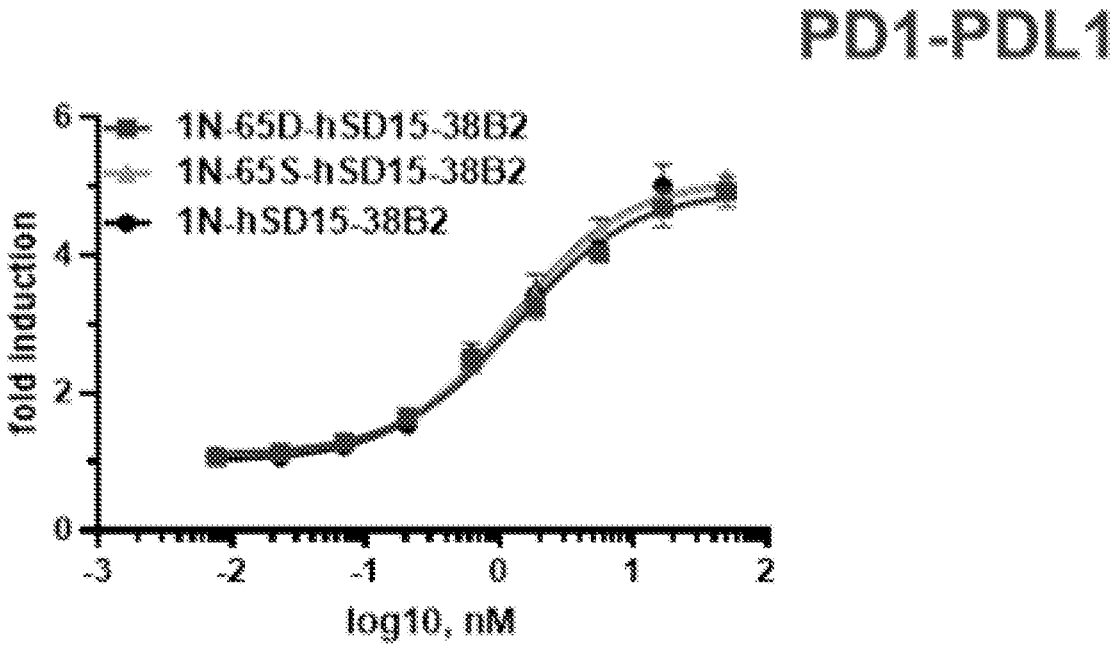

PD1-PDL1
1N-65D-hSD15-38B2
1N-65S-hSD15-38B2
1N-hSD15-38B2
fold induction
0
2
4
6
-3
-2
-1
0
1
2
log10, nM

Fig. 26C

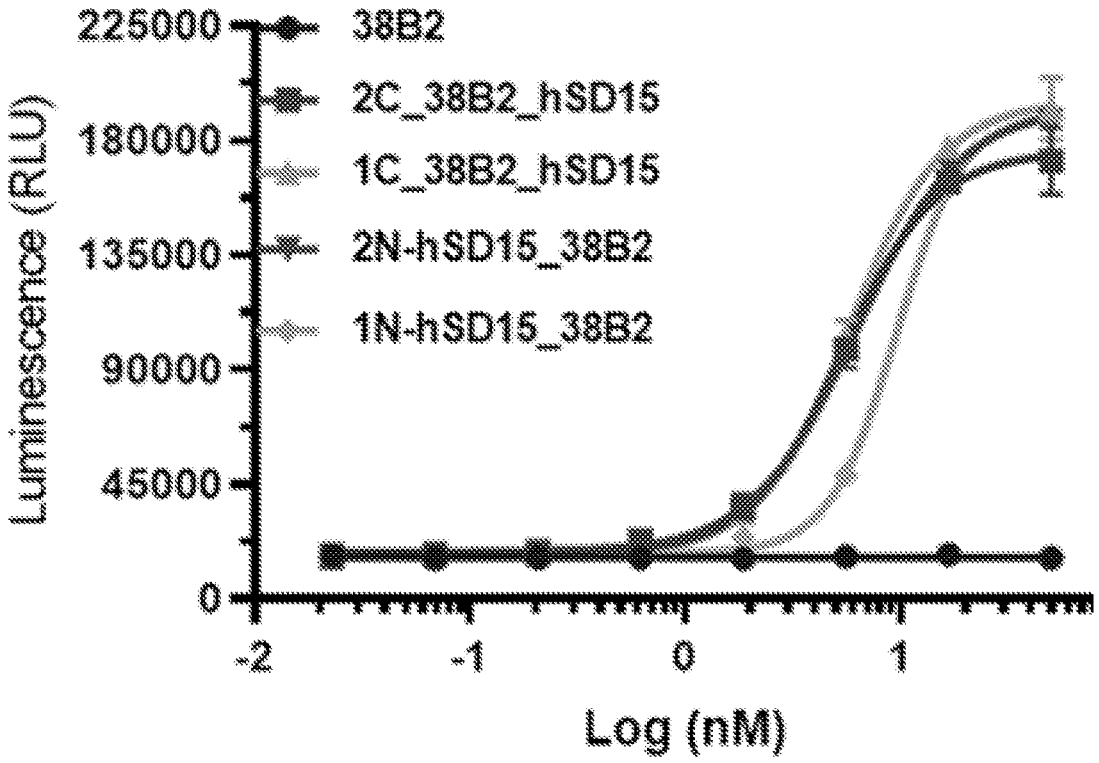


Fig. 27A

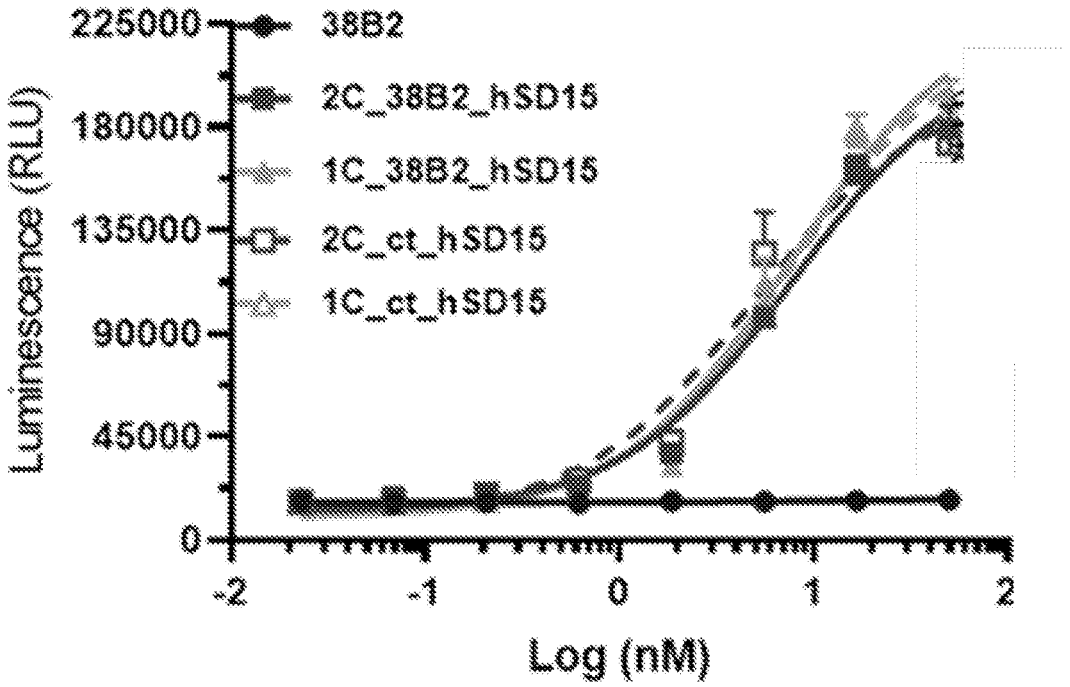


Fig. 27B

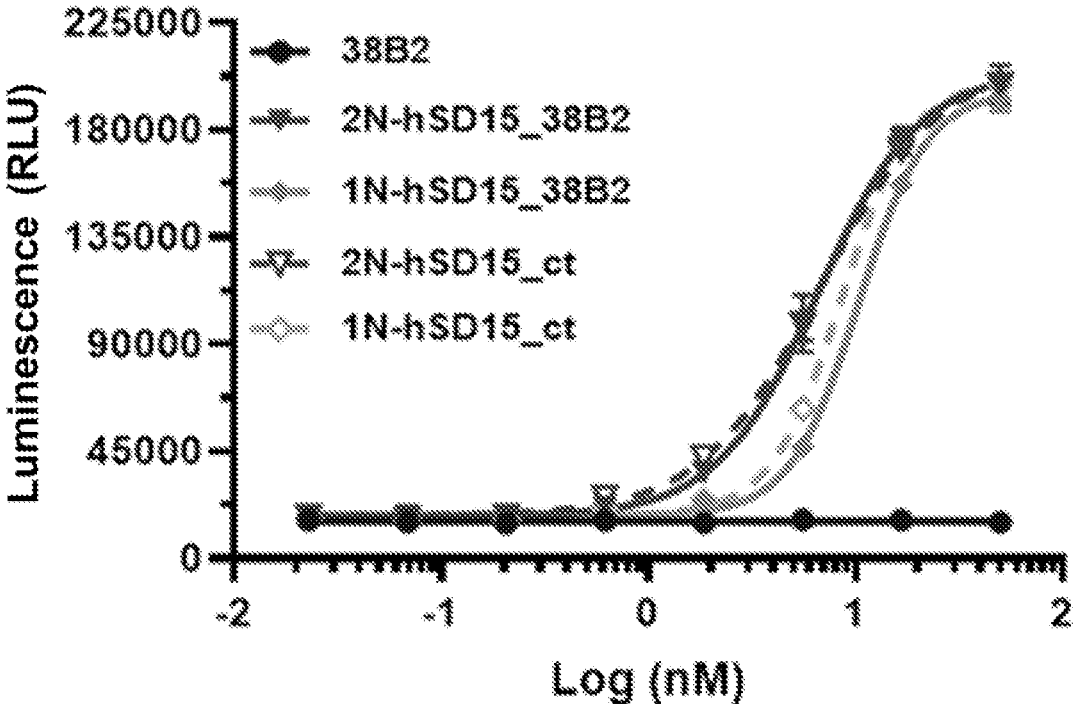

225000
180000
135000
90000
45000
0
Luminescence (RLU)
38B2
2N-hSD15_38B2
1N-hSD15_38B2
2N-hSD15_ct
1N-hSD15_ct
-2
-1
0
1
2
Log (nM)

Fig. 27C

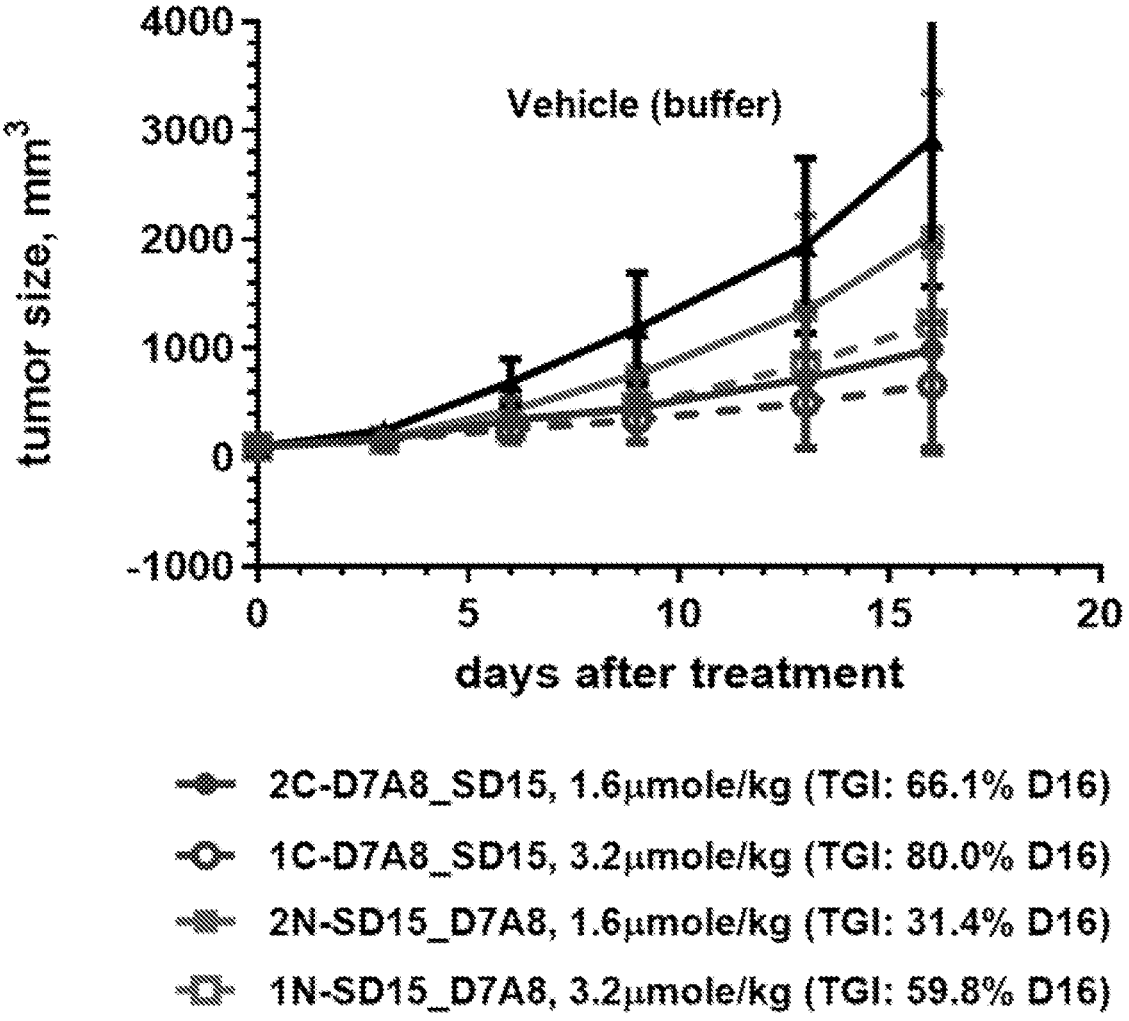

4000
3000
2000
1000
0
-1000
tumor size, mm3
Vehicle (buffer)
0
5
10
15
20
days after treatment
2C-D7A8_SD15, 1.6μmole/kg (TGI: 66.1% D16)
1C-D7A8_SD15, 3.2μmole/kg (TGI: 80.0% D16)
2N-SD15_D7A8, 1.6μmole/kg (TGI: 31.4% D16)
1N-SD15_D7A8, 3.2μmole/kg (TGI: 59.8% D16)

Fig. 28

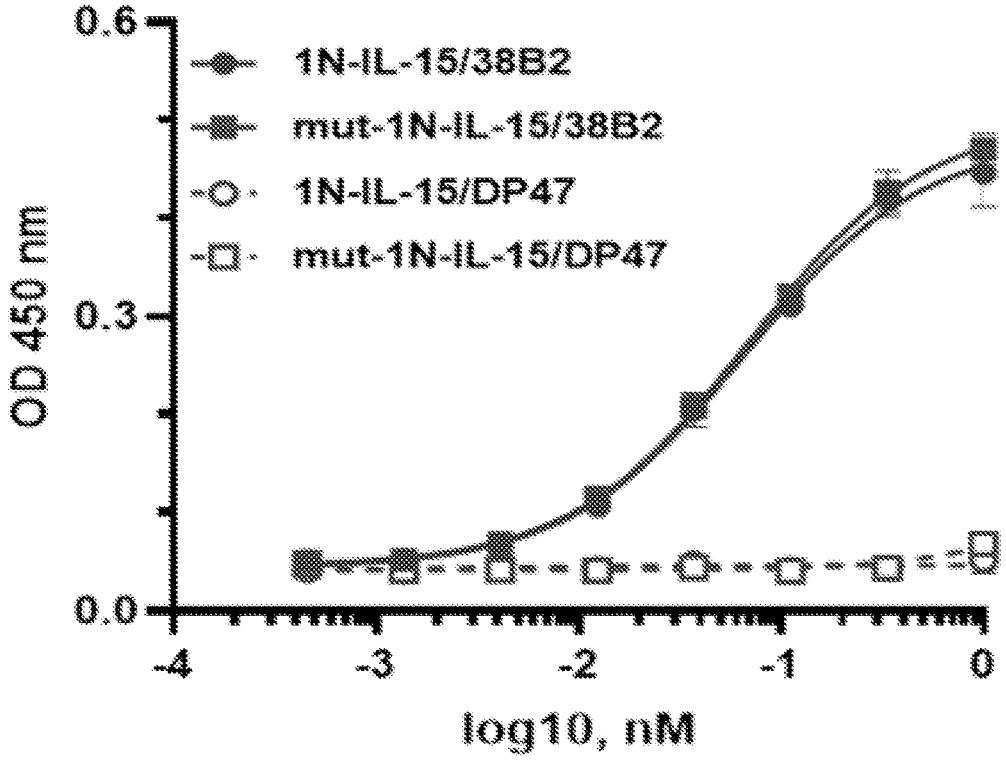


Fig. 29A

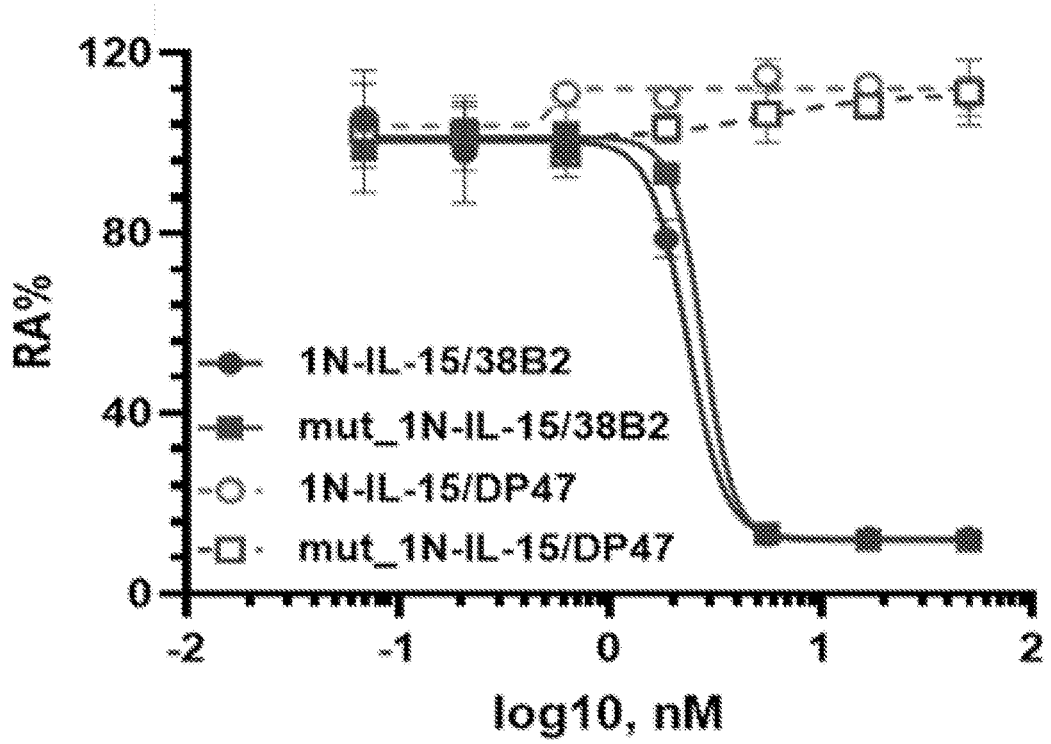


Fig. 29B

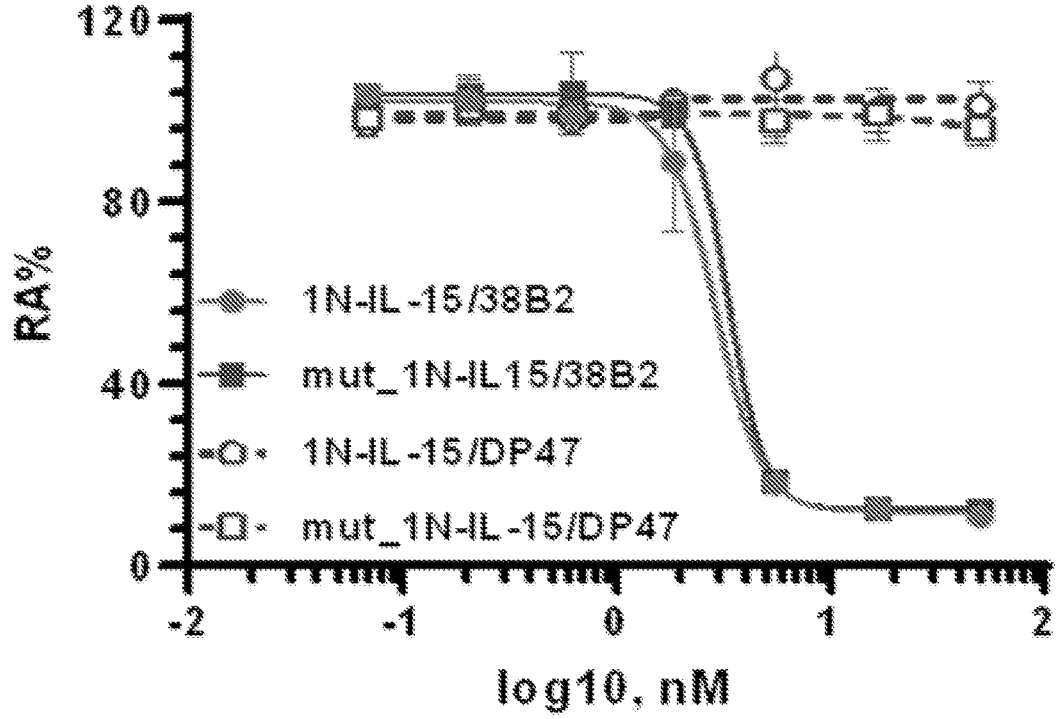


Fig. 29C

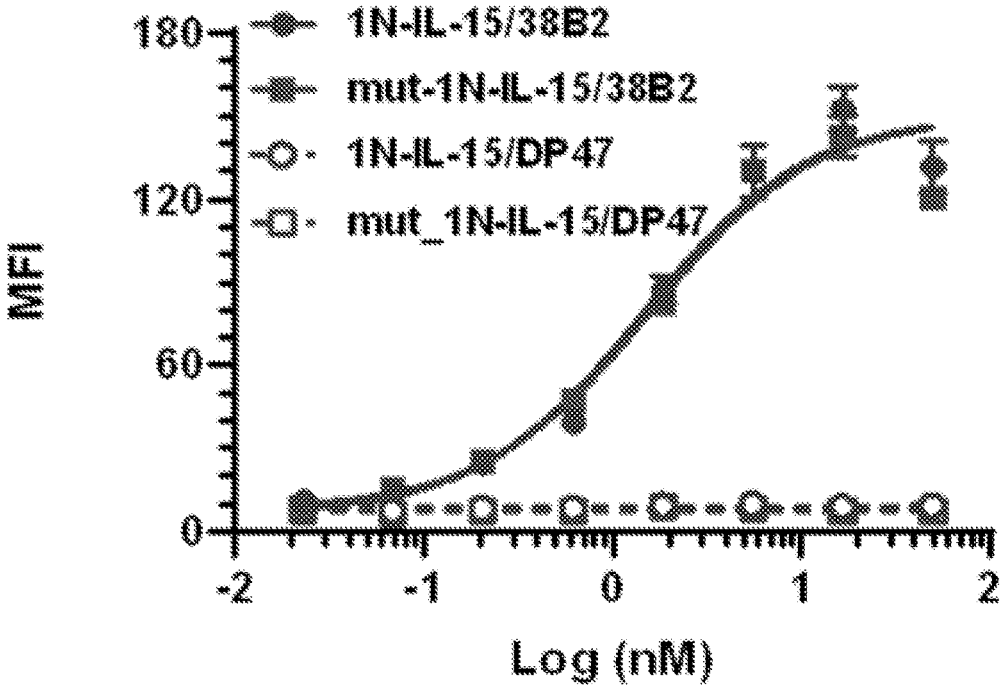


Fig. 29D

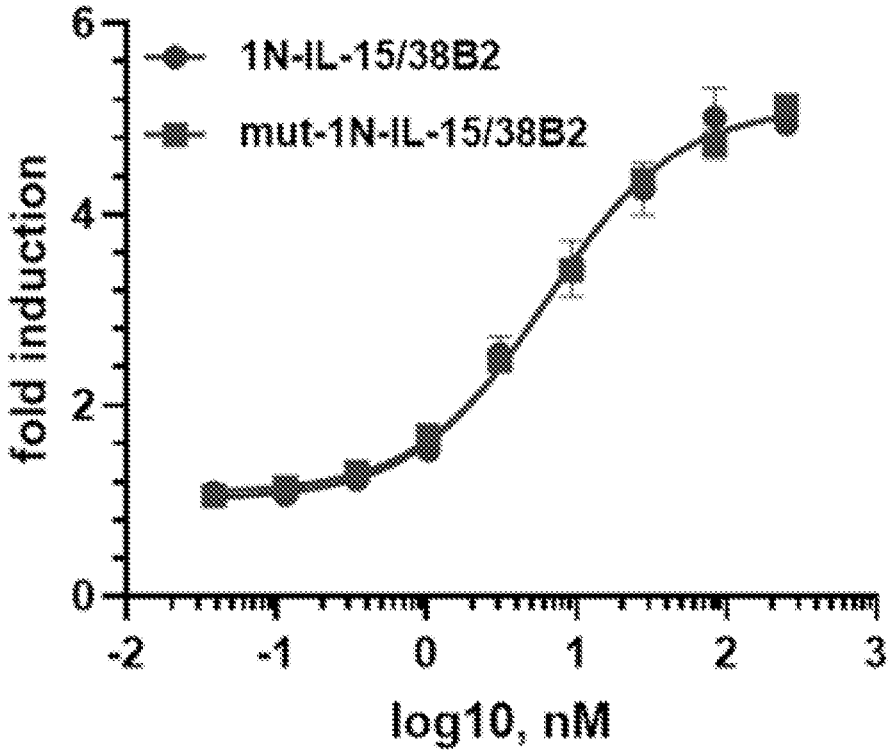


Fig. 29E

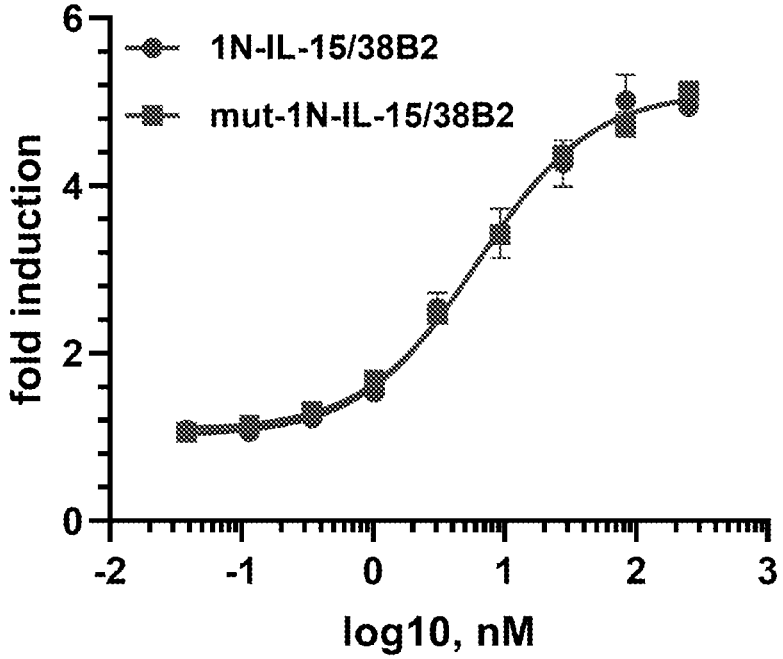


Fig. 29F

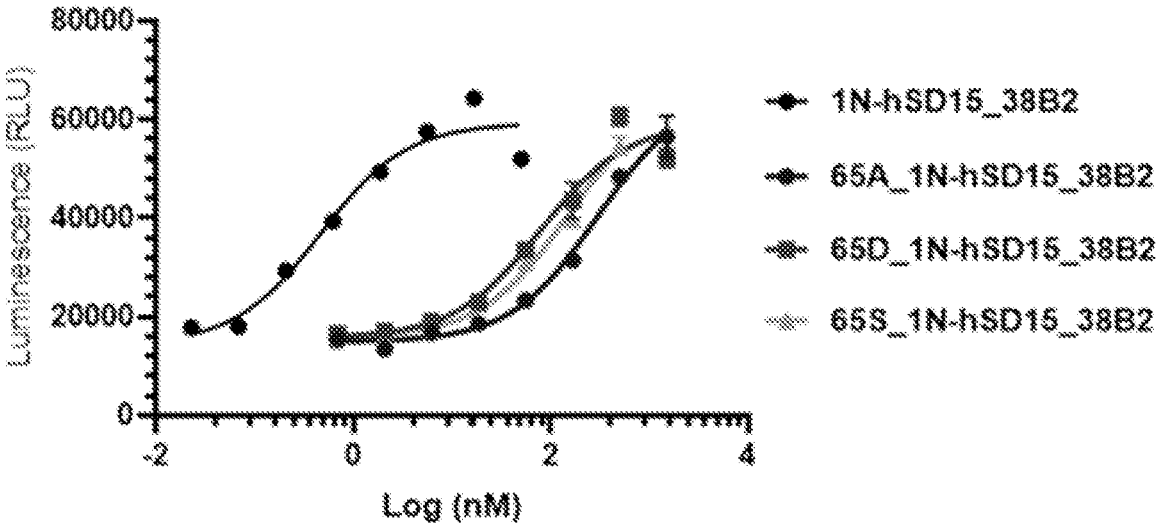


Fig. 30A

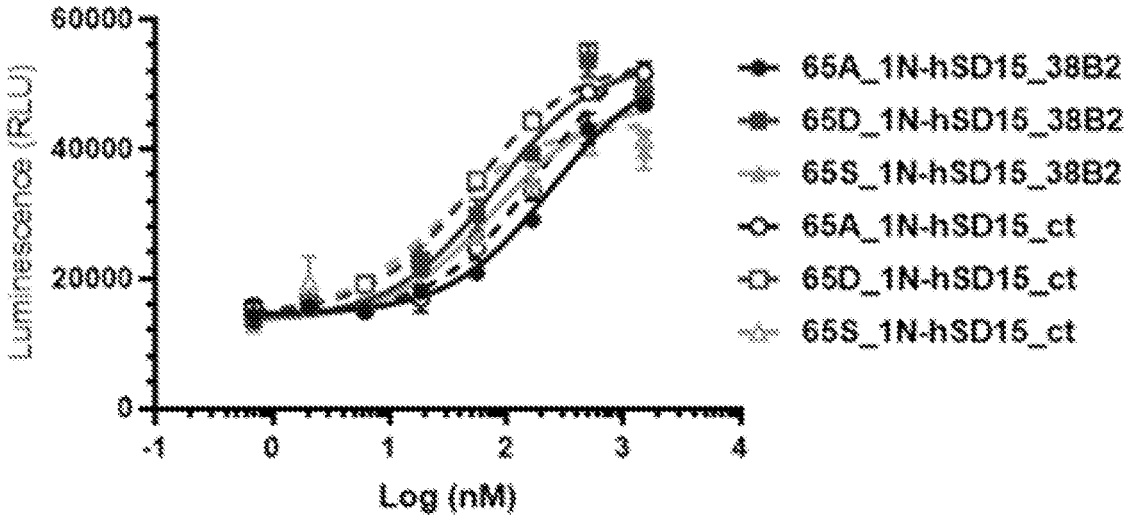


Fig. 30B

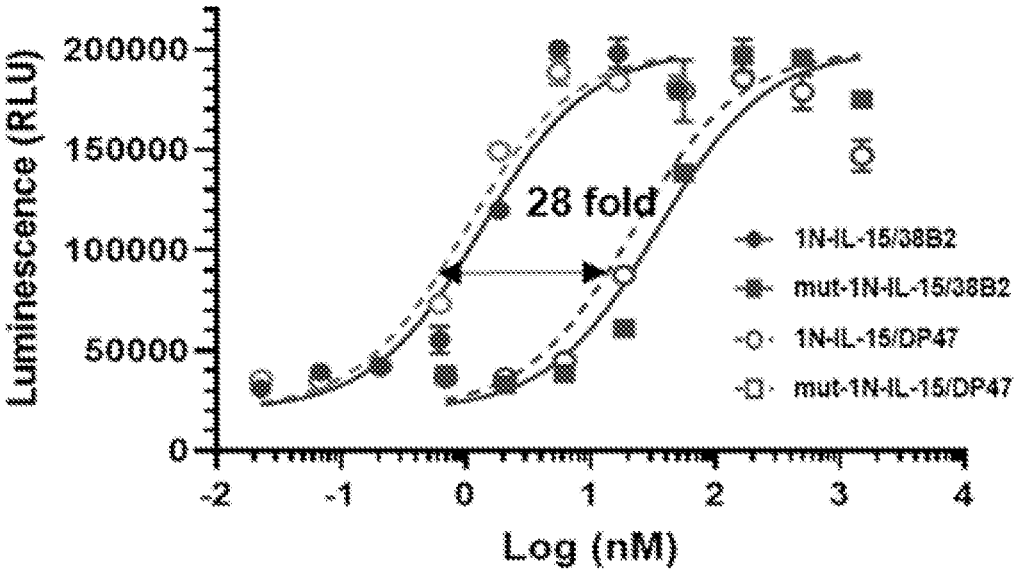


Fig. 30C

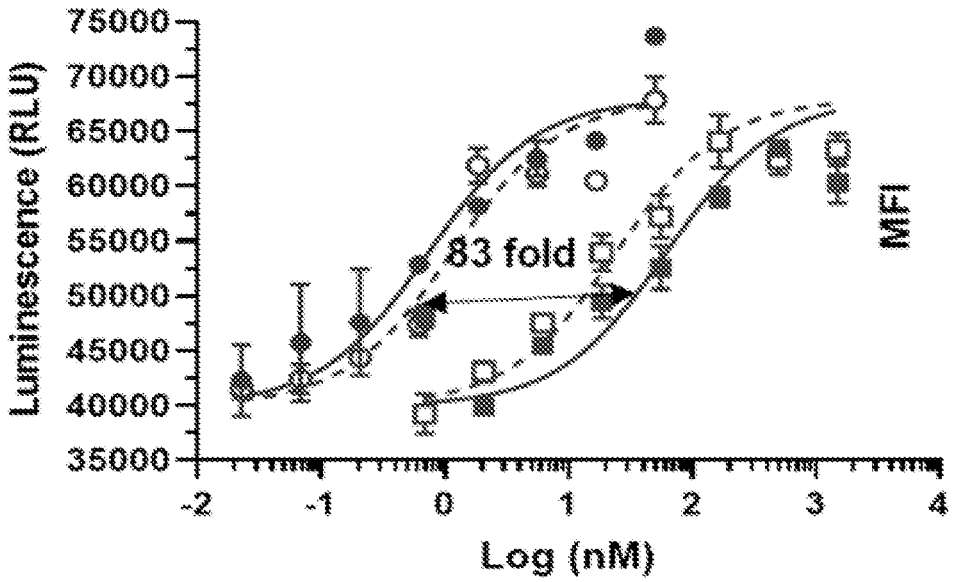


Fig. 30D

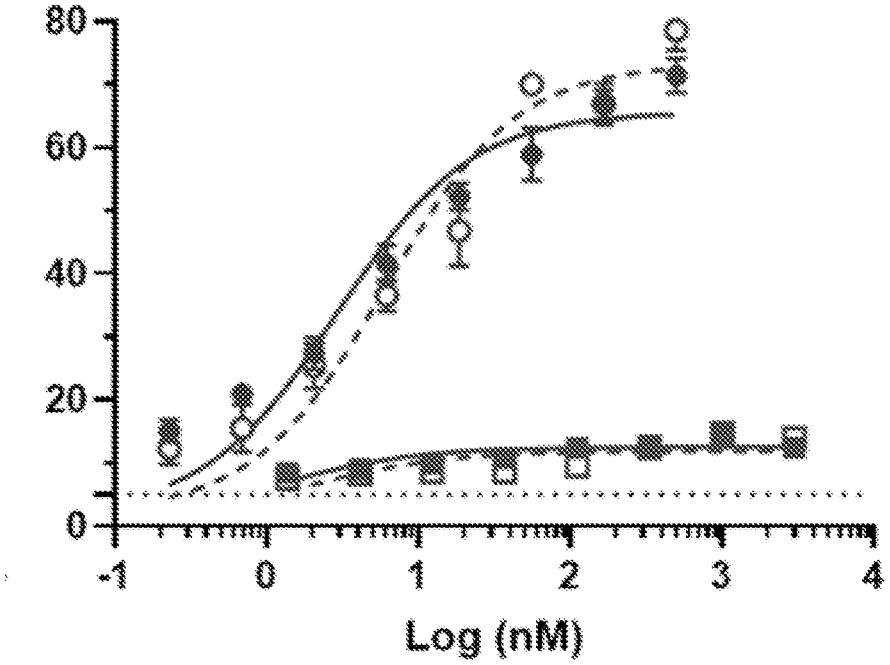


Fig. 30E

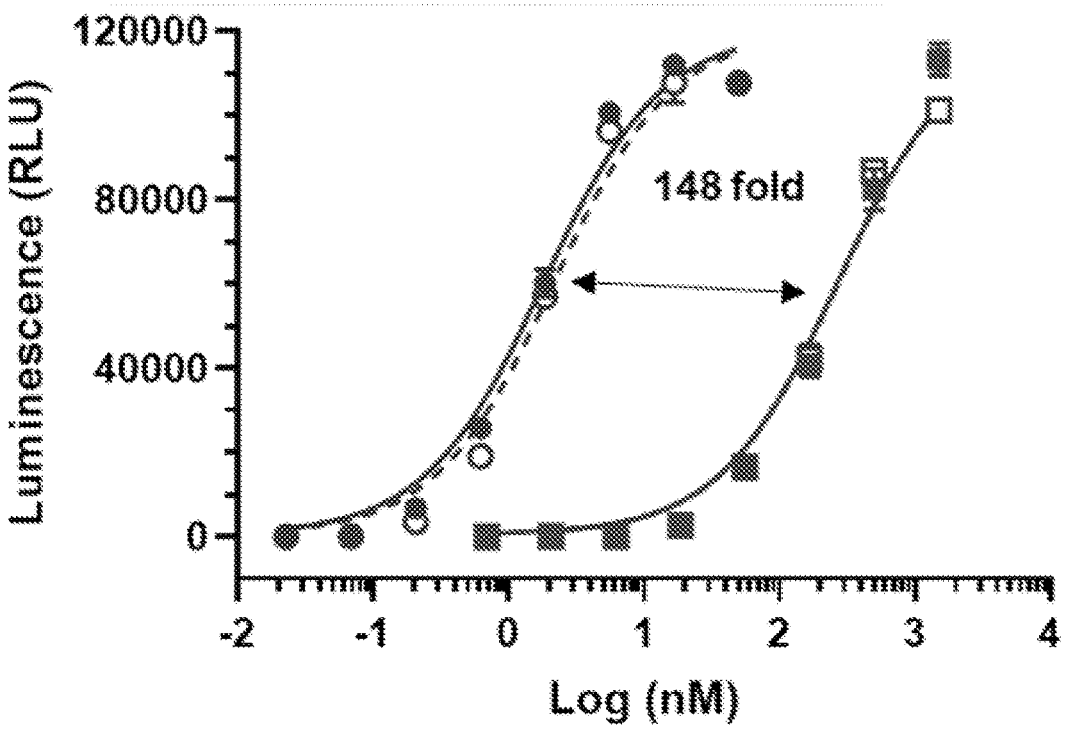


Fig. 31A

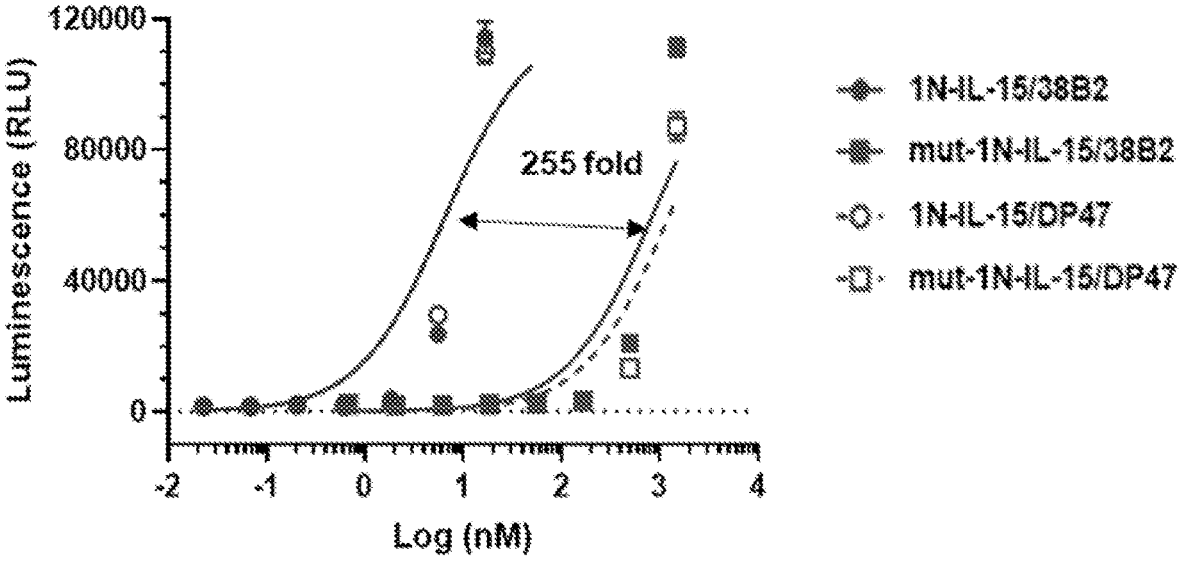


Fig. 31B

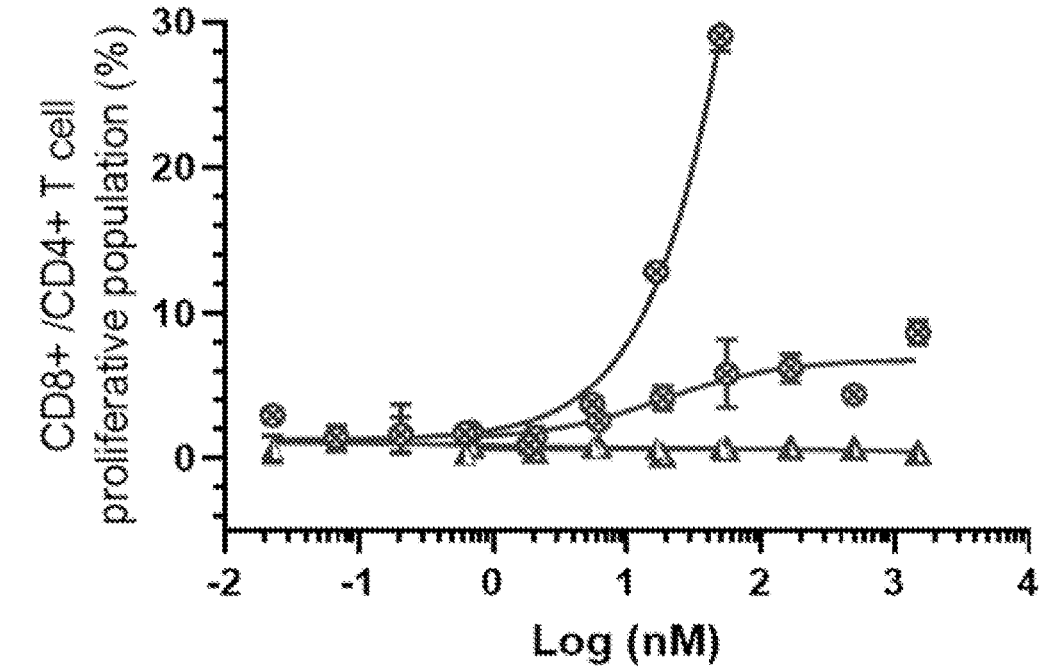


Fig. 31C

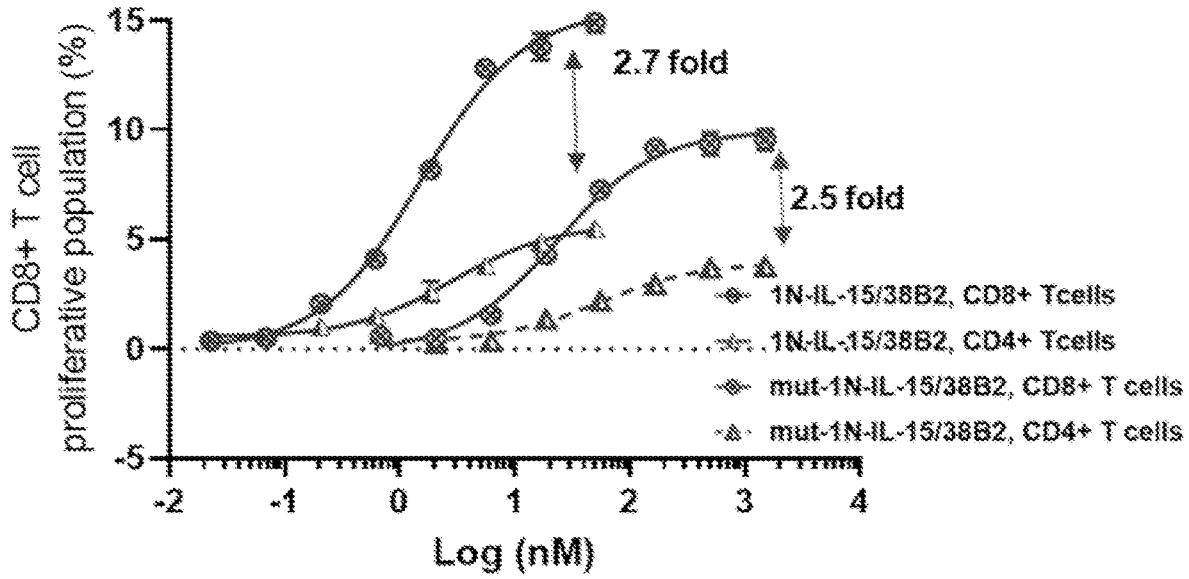


Fig. 31D

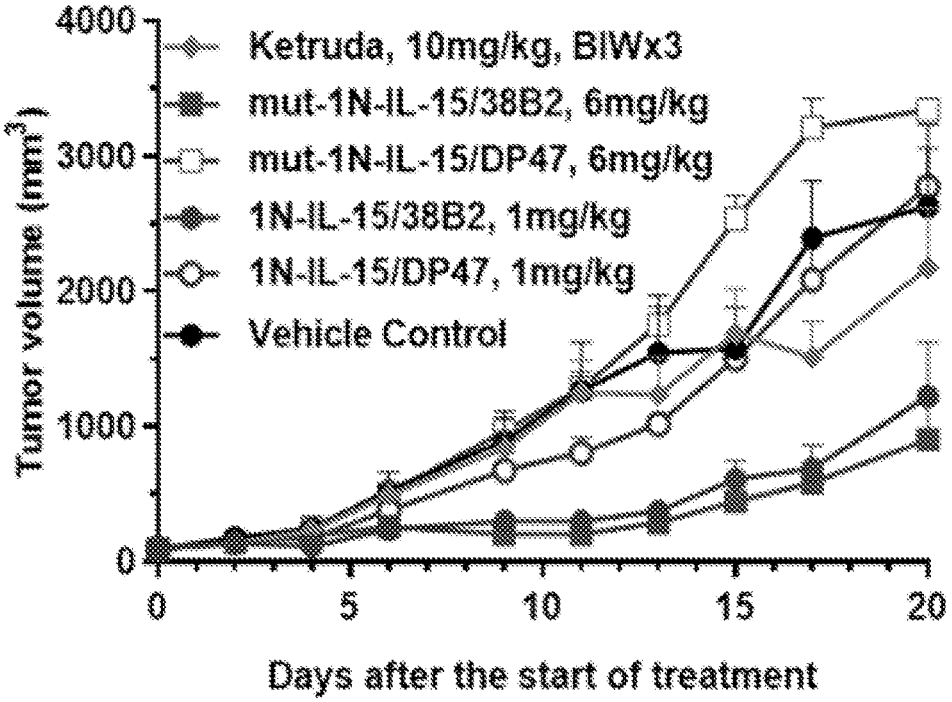


Fig. 32A

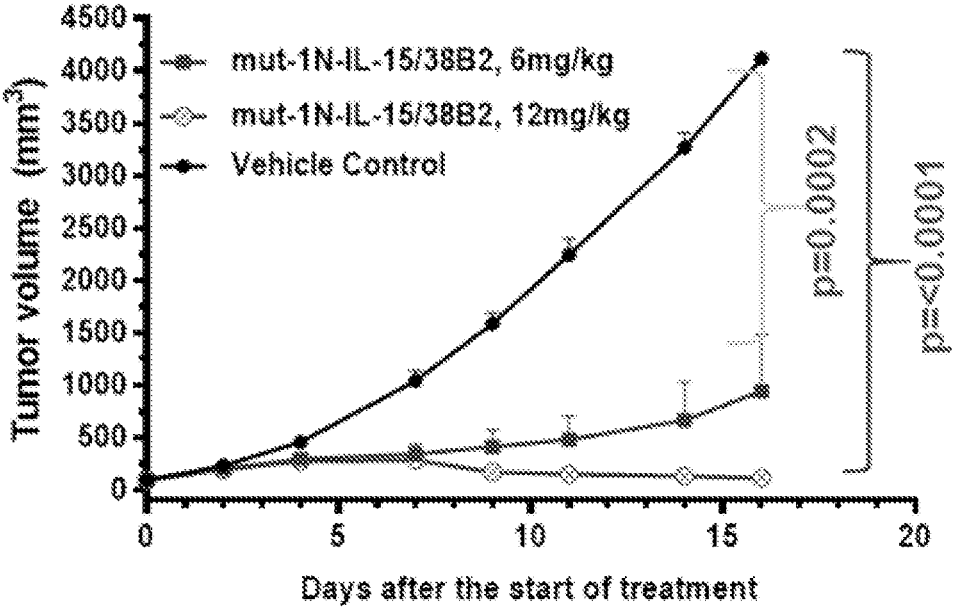


Fig. 32B

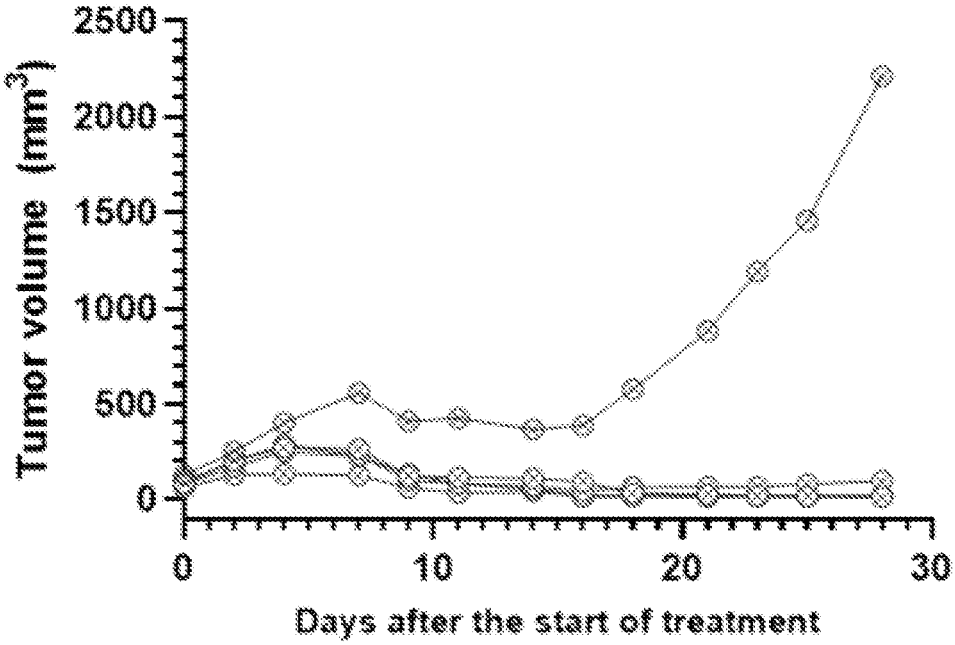


Fig. 32C

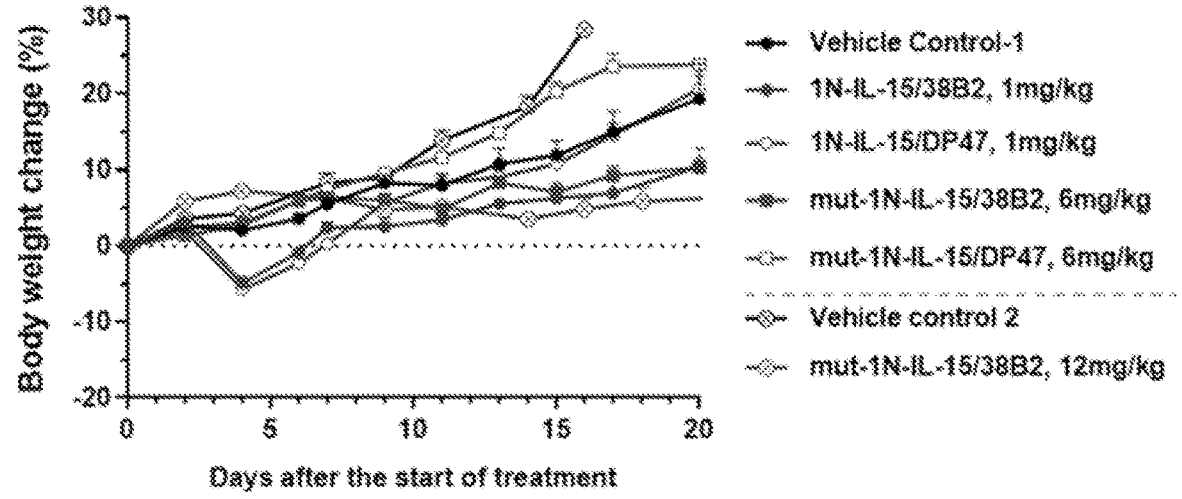


Fig. 32D

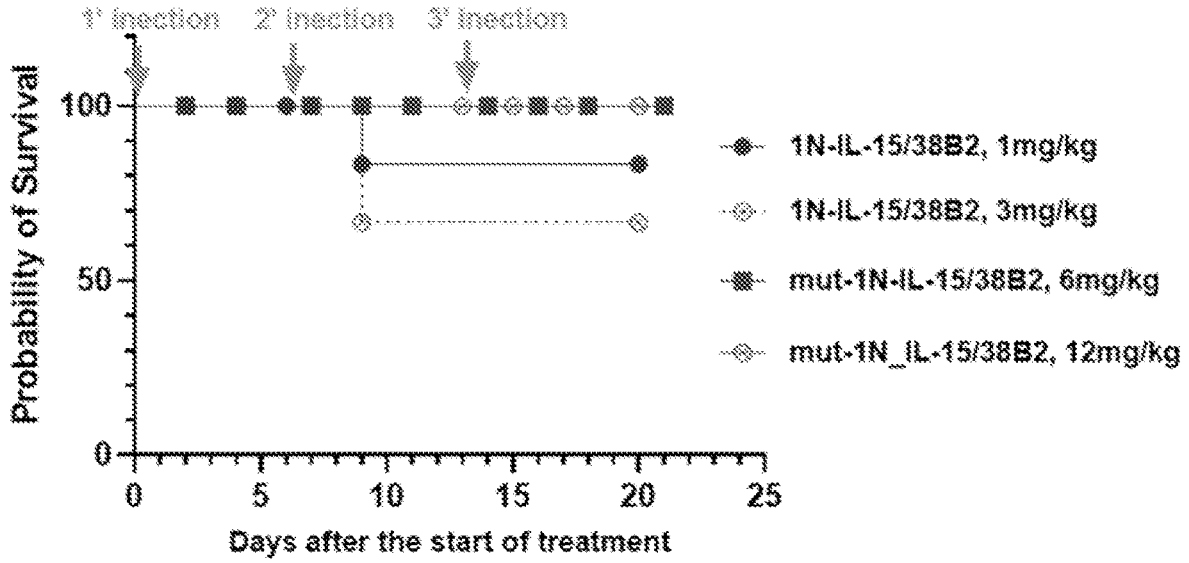


Fig. 32E

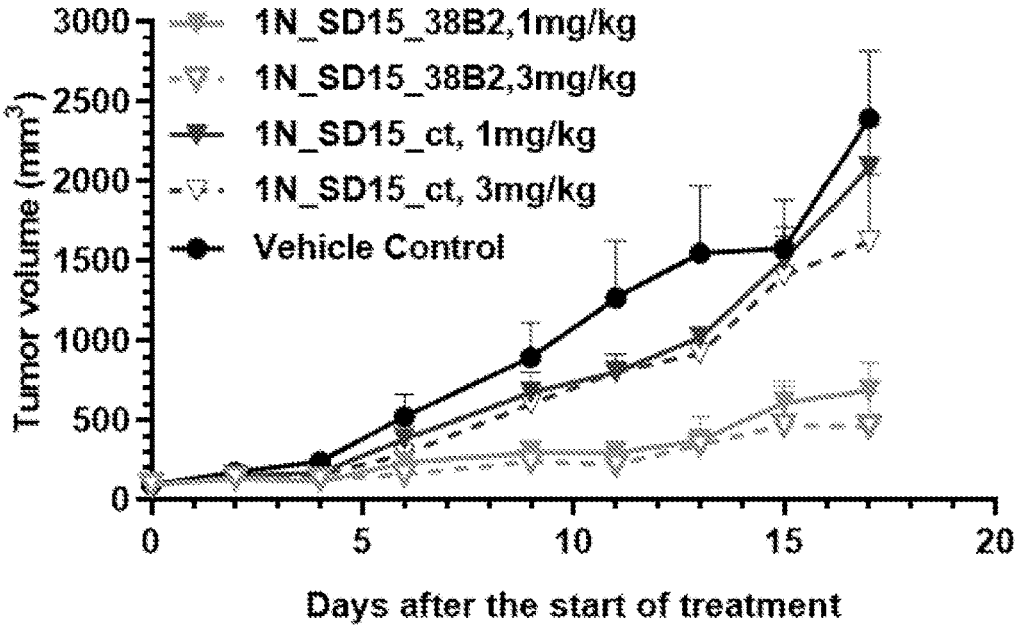


Fig. 32F

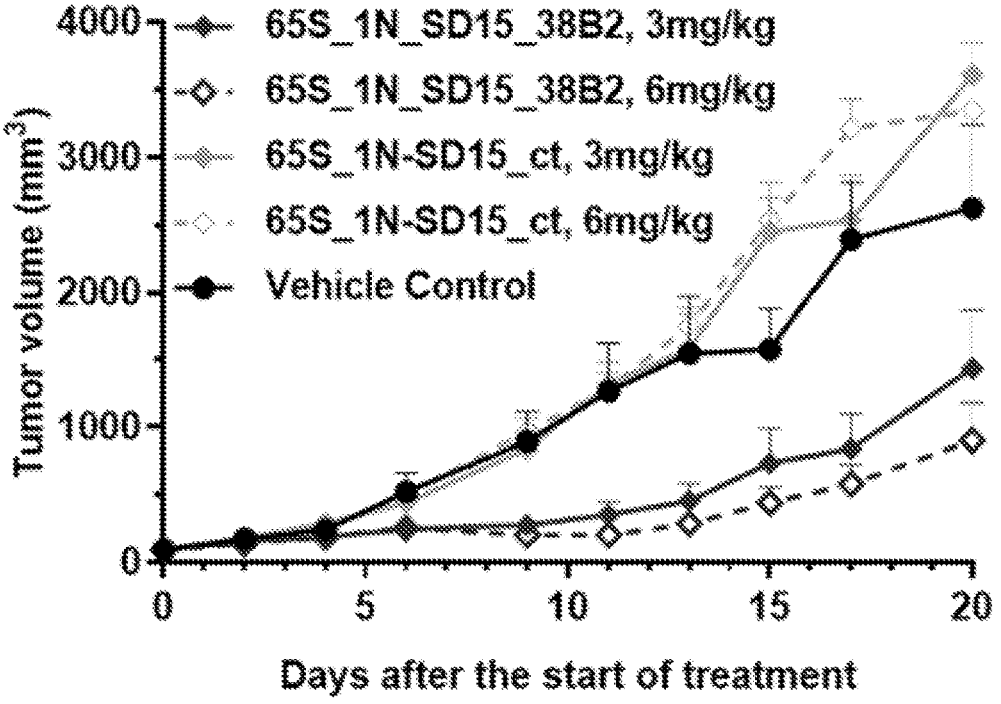


Fig. 32G

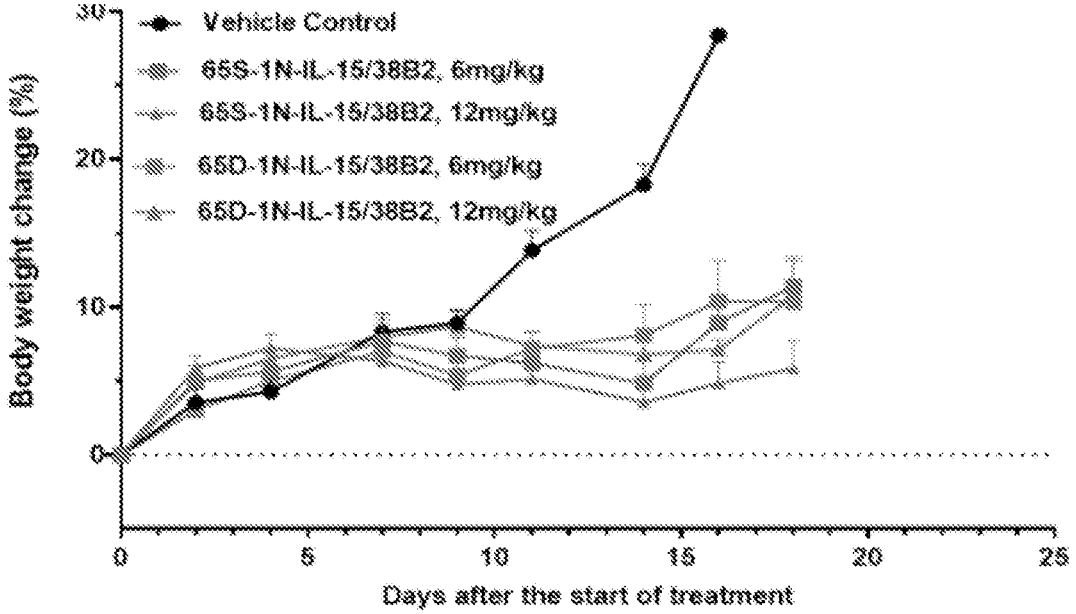


Fig. 32H

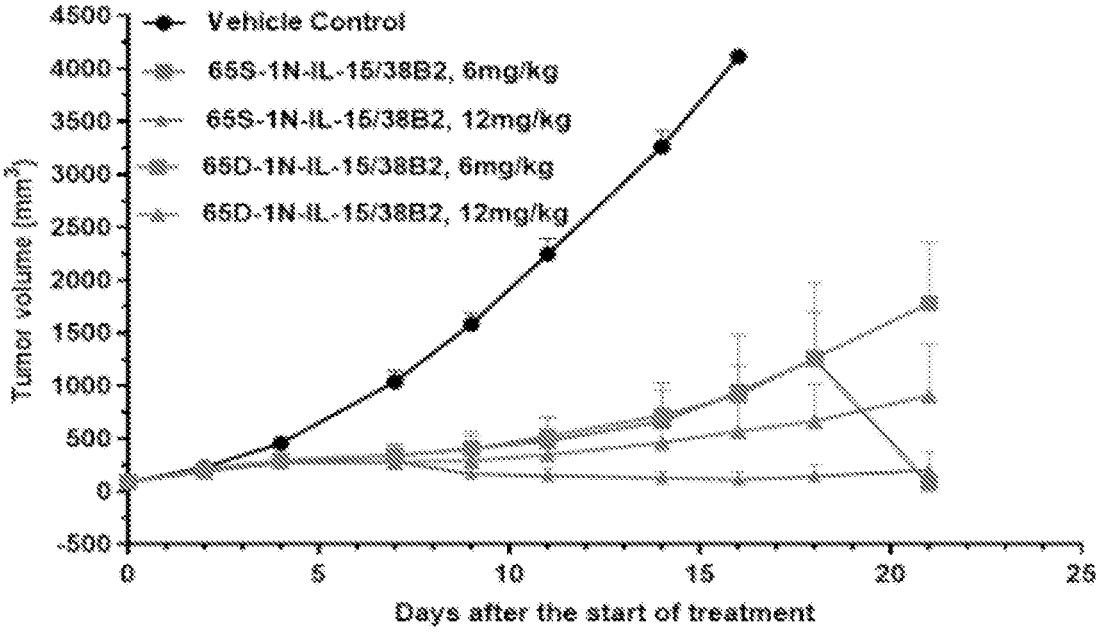


Fig. 32I

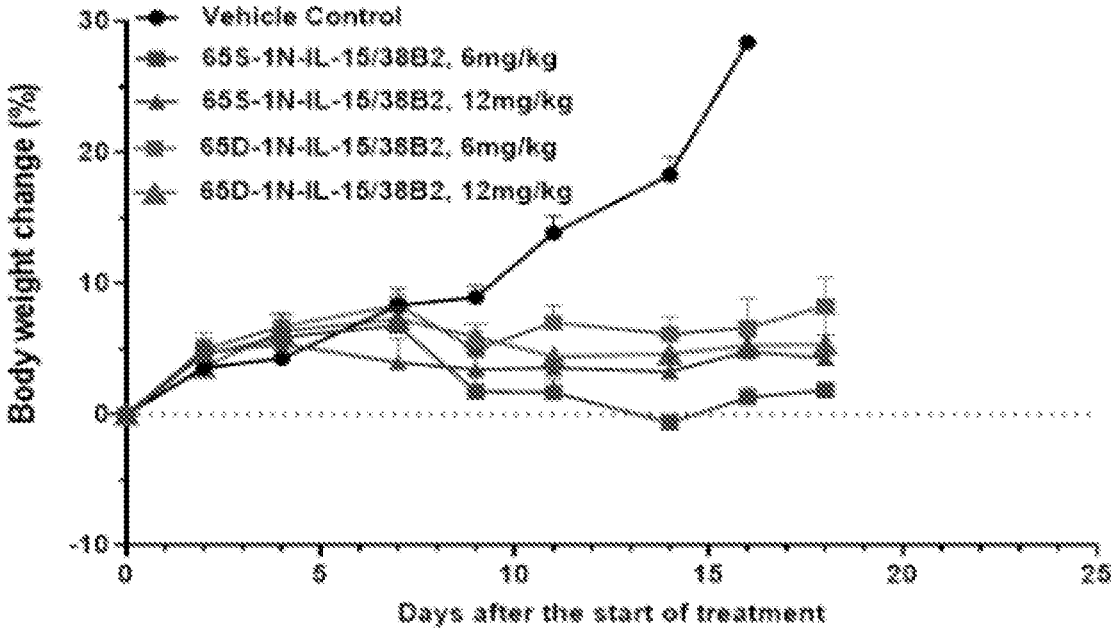


Fig. 32J

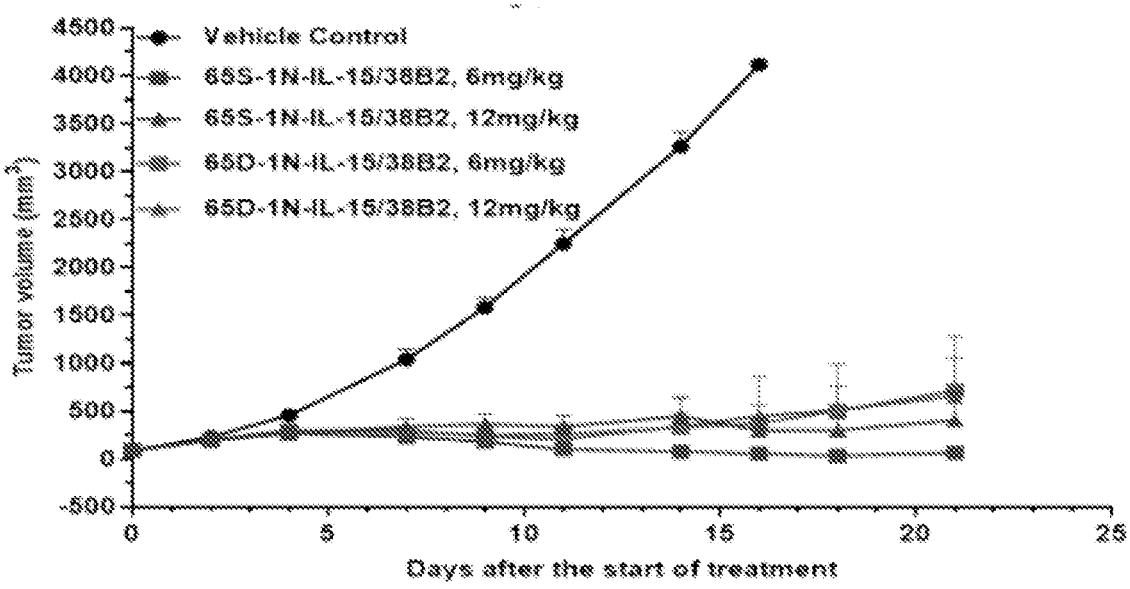


Fig. 32K

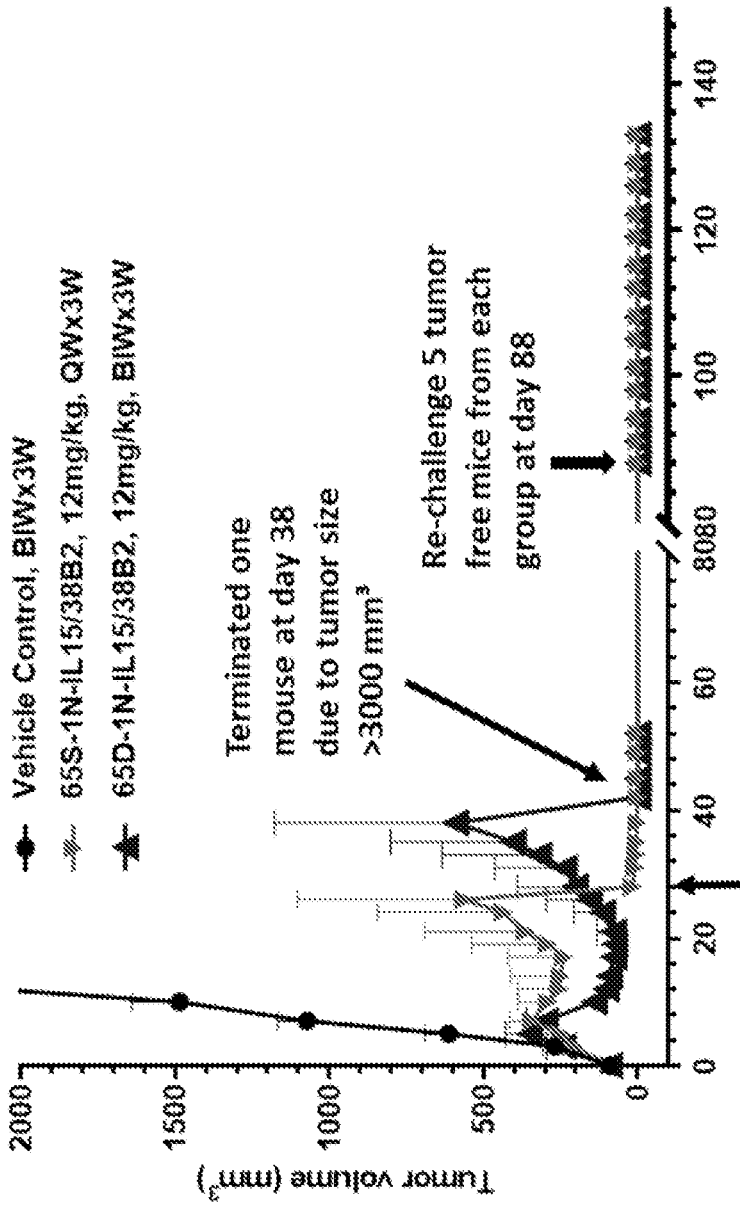

Vehicle Control, BIWx3W
65S-1N-IL15/38B2, 12mg/kg, QWx3W
65D-1N-IL15/38B2, 12mg/kg, BIWx3W
Terminated one mouse at day 38 due to tumor size >3000 mm³
Re-challenge 5 tumor free mice from each group at day 88
Terminated one mouse at day 26 due to tumor size >3000 mm³
Tumor volume (mm³)
Days after the start of treatment
2000
1500
1000
500
0
0
20
40
60
80
100
120
140

Fig. 33

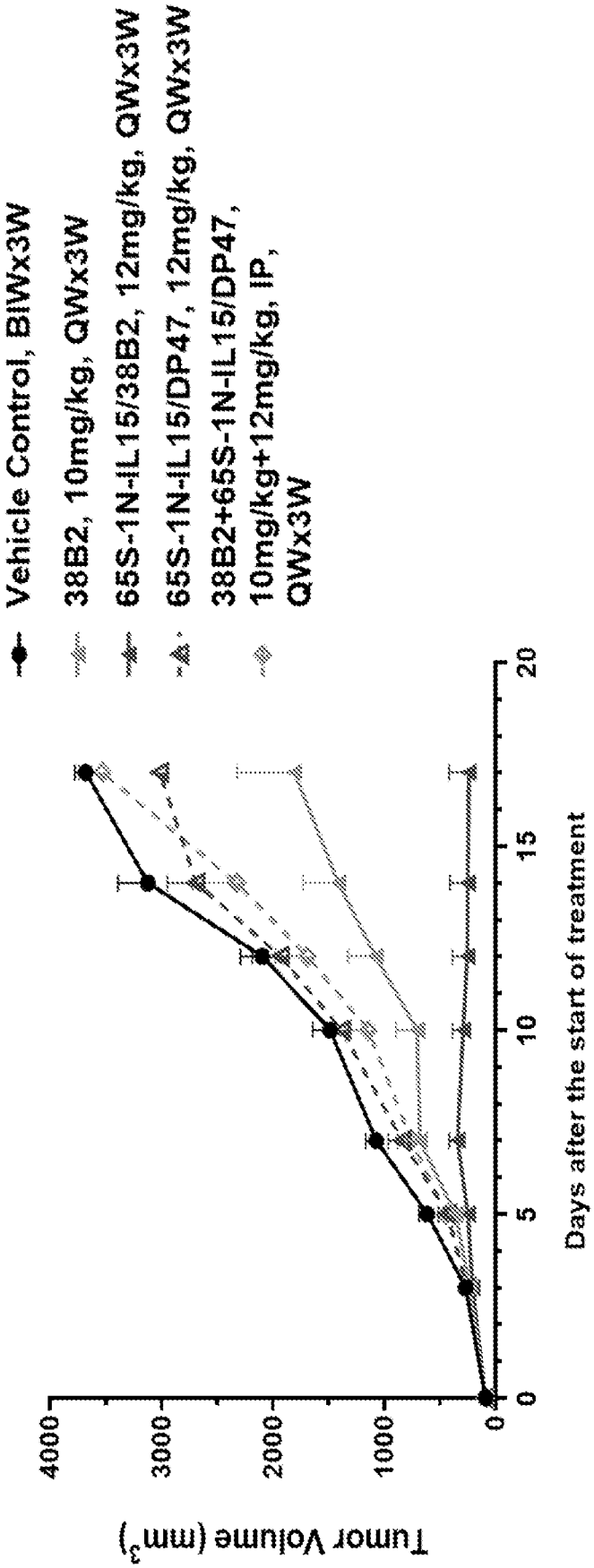

Vehicle Control, BIWx3W
38B2, 10mg/kg, QWx3W
65S-1N-IL15/38B2, 12mg/kg, QWx3W
65S-1N-IL15/DP47, 12mg/kg, QWx3W
38B2+65S-1N-IL15/DP47, 10mg/kg+12mg/kg, IP, QWx3W
Tumor Volume (mm³)
4000
3000
2000
1000
0
0
5
10
15
20
Days after the start of treatment

Fig. 34A

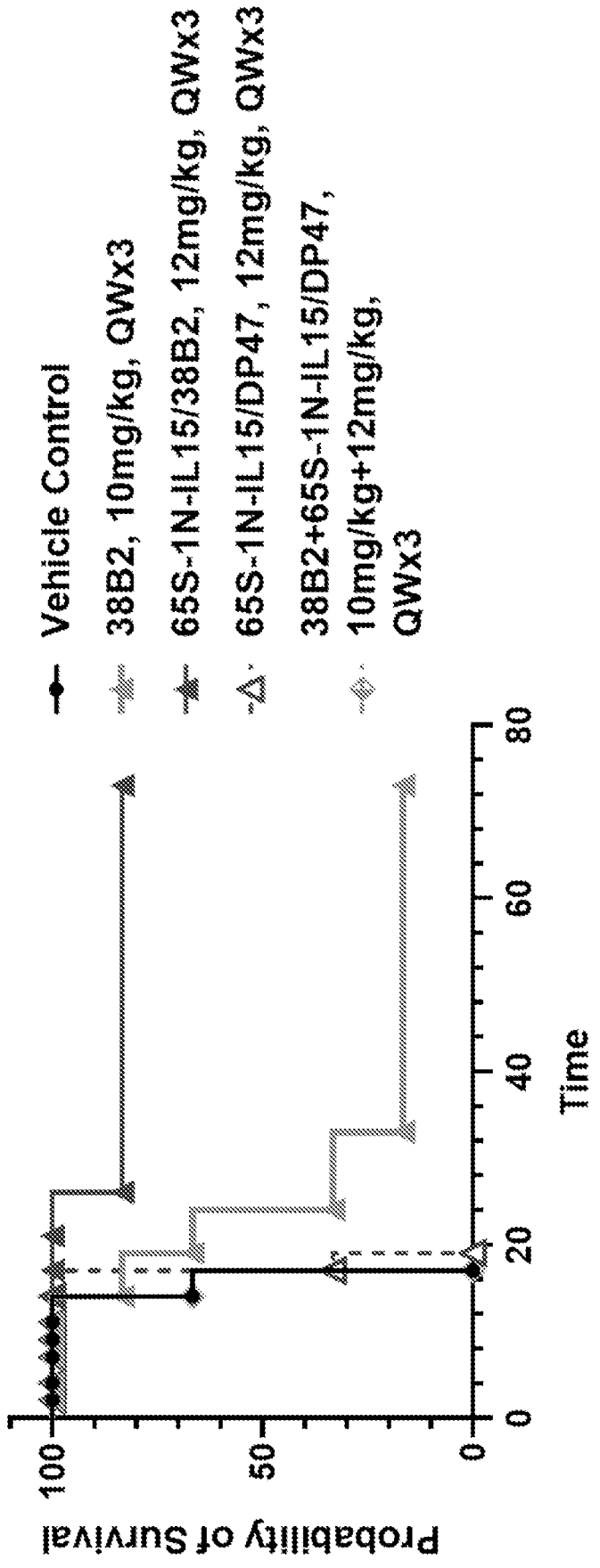

Vehicle Control
38B2, 10mg/kg, QWx3
65S-1N-IL15/38B2, 12mg/kg, QWx3
65S-1N-IL15/DP47, 12mg/kg, QWx3
38B2+65S-1N-IL15/DP47, 10mg/kg+12mg/kg, QWx3
Probability of Survival
100
50
0
0
20
40
60
80
Time

Fig. 34B

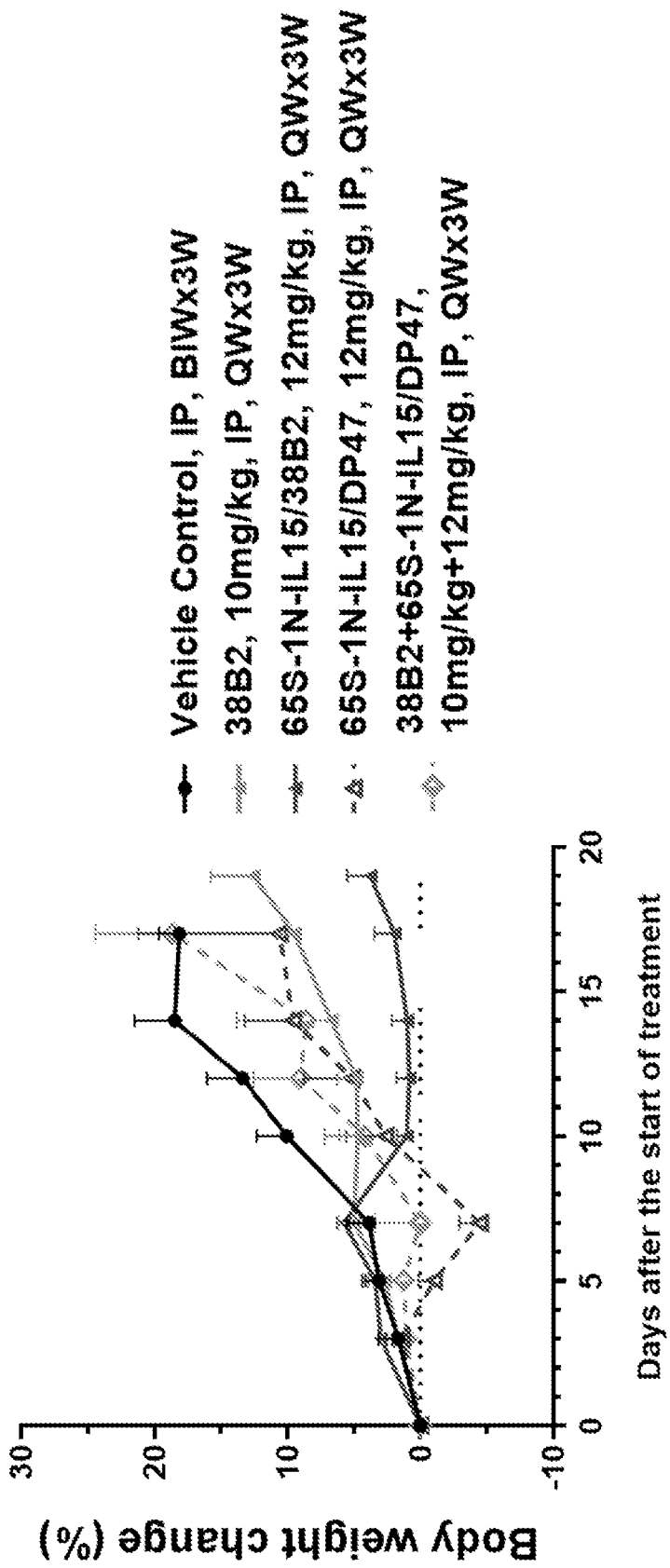

Body weight change (%)
30
20
10
0
-10
0
5
10
15
20
Days after the start of treatment
Vehicle Control, IP, BIWx3W
38B2, 10mg/kg, IP, QWx3W
65S-1N-IL15/38B2, 12mg/kg, IP, QWx3W
65S-1N-IL15/DP47, 12mg/kg, IP, QWx3W
38B2+65S-1N-IL15/DP47, 10mg/kg+12mg/kg, IP, QWx3W

Fig. 34C

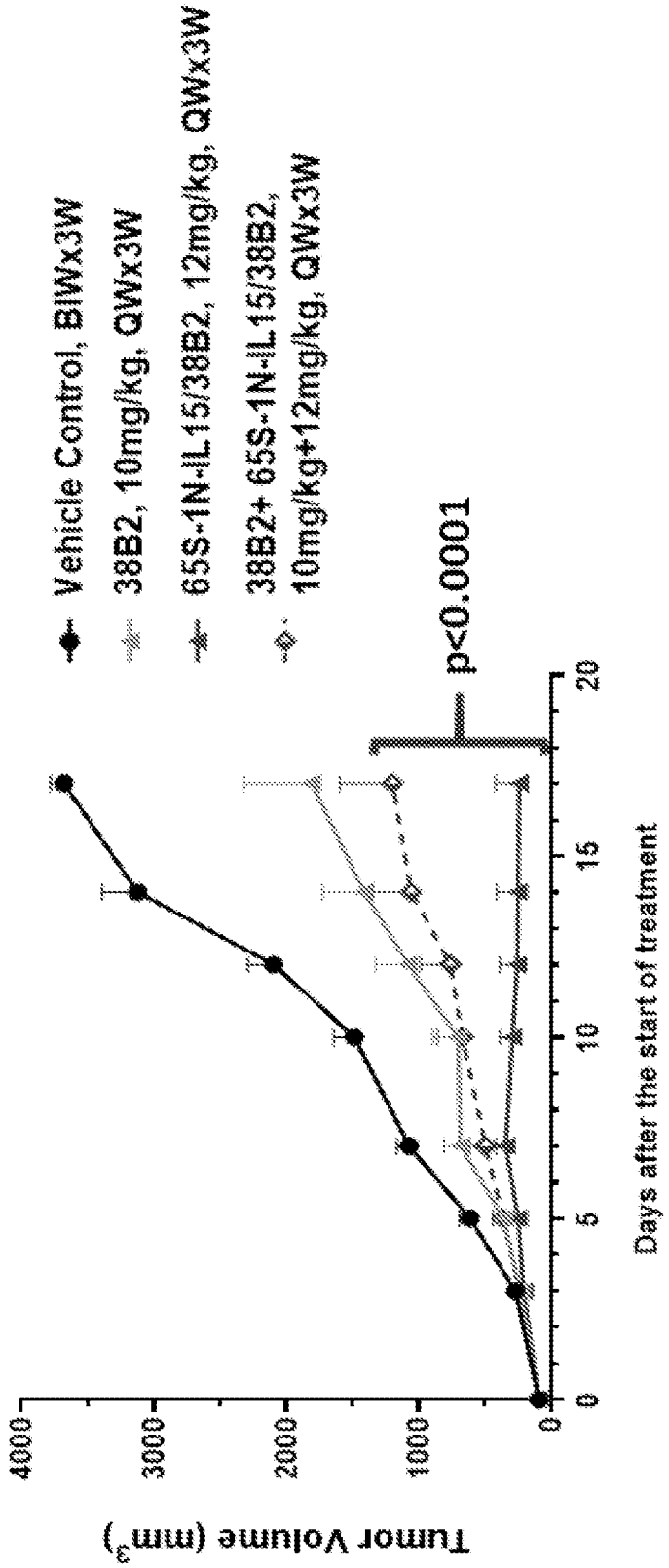

Vehicle Control, BIWx3W
38B2, 10mg/kg, QWx3W
65S-1N-IL15/38B2, 12mg/kg, QWx3W
38B2+ 65S-1N-IL15/38B2, 10mg/kg+12mg/kg, QWx3W
p<0.0001
Tumor Volume (mm³)
4000
3000
2000
1000
0
0
5
10
15
20
Days after the start of treatment

Fig. 35A

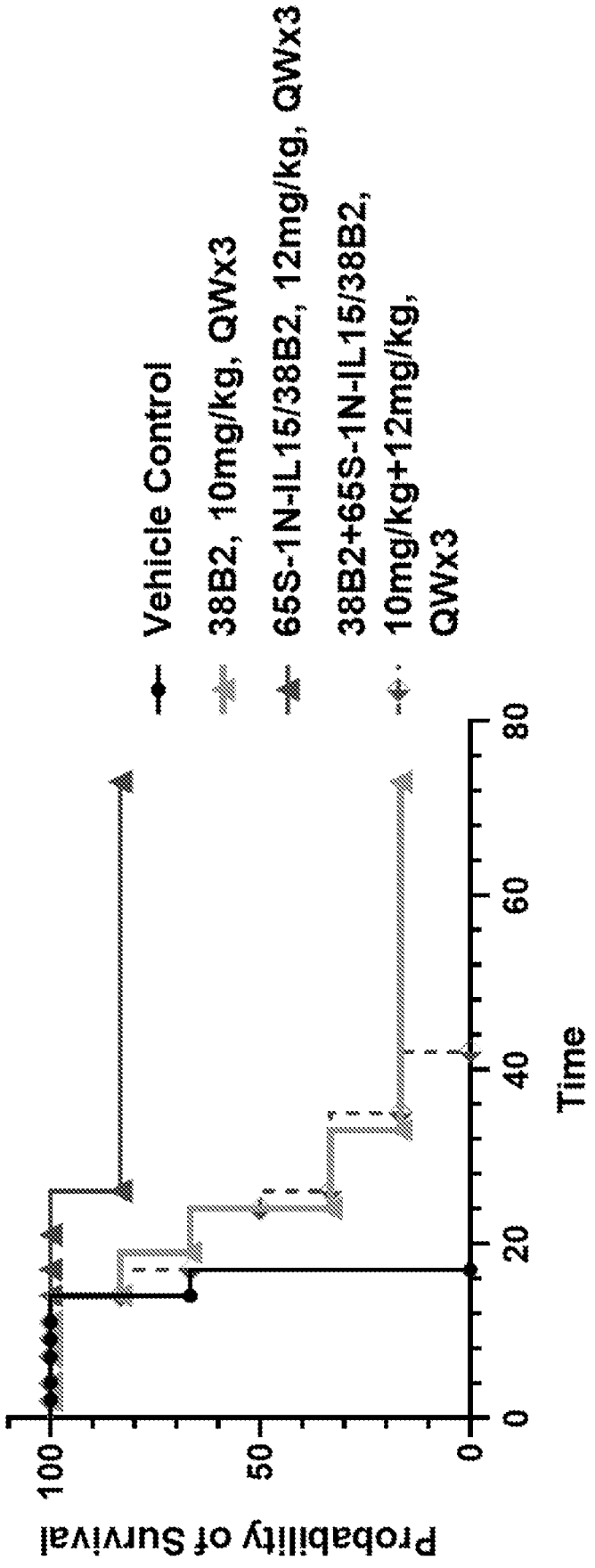

Probability of Survival
100
50
0
0
20
40
60
80
Time
Vehicle Control
38B2, 10mg/kg, QWx3
65S-1N-IL15/38B2, 12mg/kg, QWx3
38B2+65S-1N-IL15/38B2, 10mg/kg+12mg/kg, QWx3

Fig. 35B

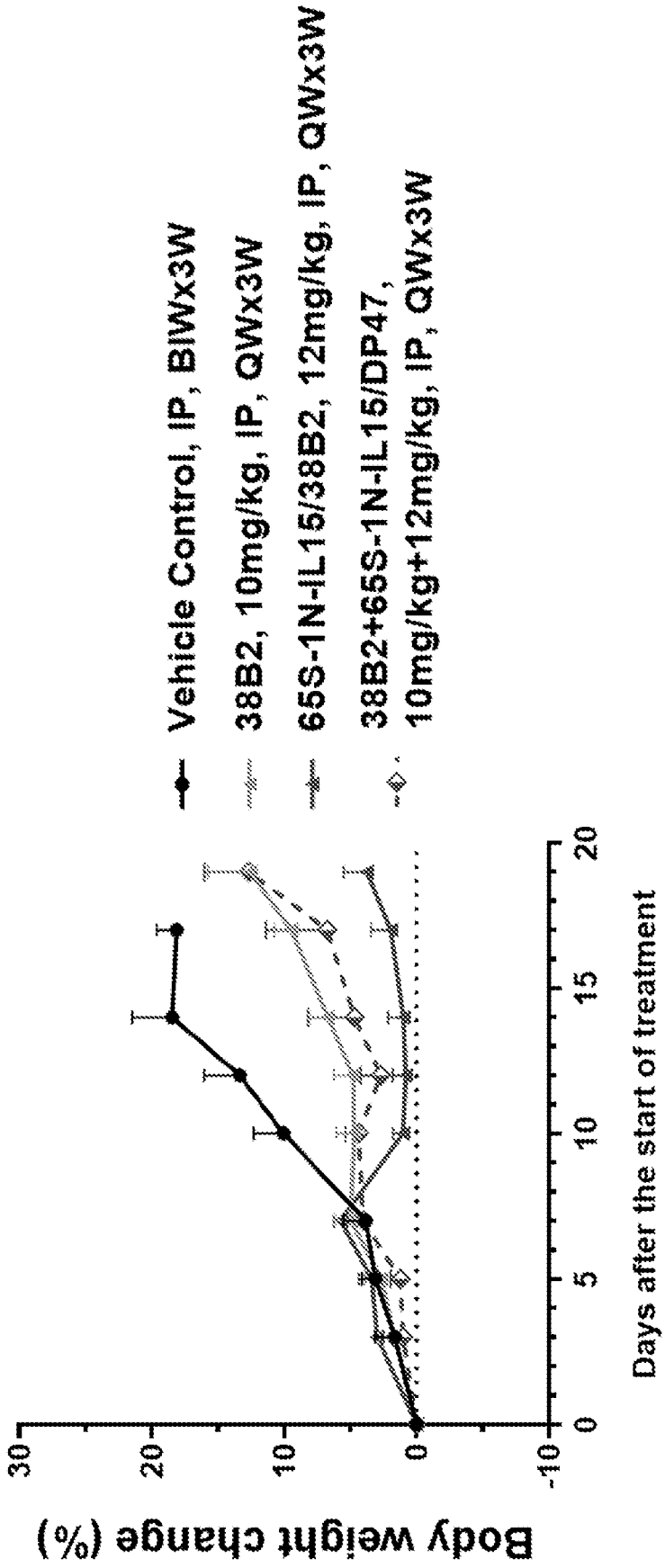

Body weight change (%)
30
20
10
0
-10
0
5
10
15
20
Days after the start of treatment
Vehicle Control, IP, BIWx3W
38B2, 10mg/kg, IP, QWx3W
65S-1N-IL15/38B2, 12mg/kg, IP, QWx3W
38B2+65S-1N-IL15/DP47, 10mg/kg+12mg/kg, IP, QWx3W

Fig. 35C

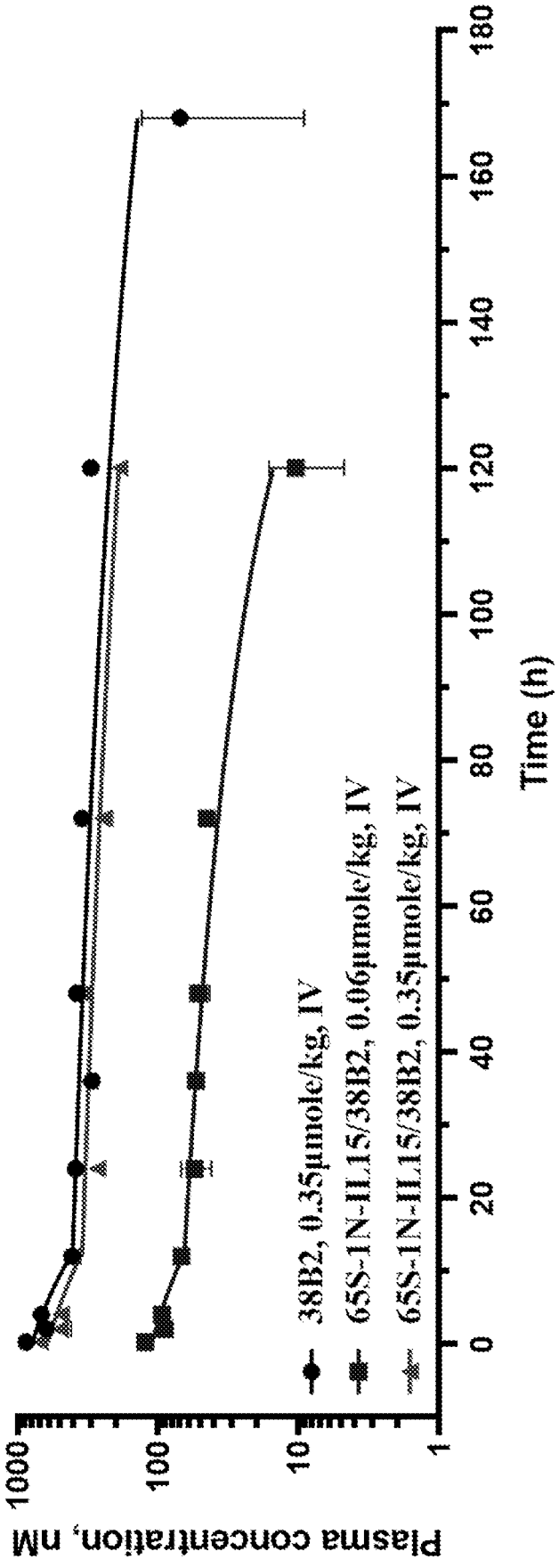

Plasma concentration, nM
1000
100
10
1
0
20
40
60
80
100
120
140
160
180
Time (h)
38B2, 0.35μmole/kg, IV
65S-1N-IL15/38B2, 0.06μmole/kg, IV
65S-1N-IL15/38B2, 0.35μmole/kg, IV

Fig. 36A

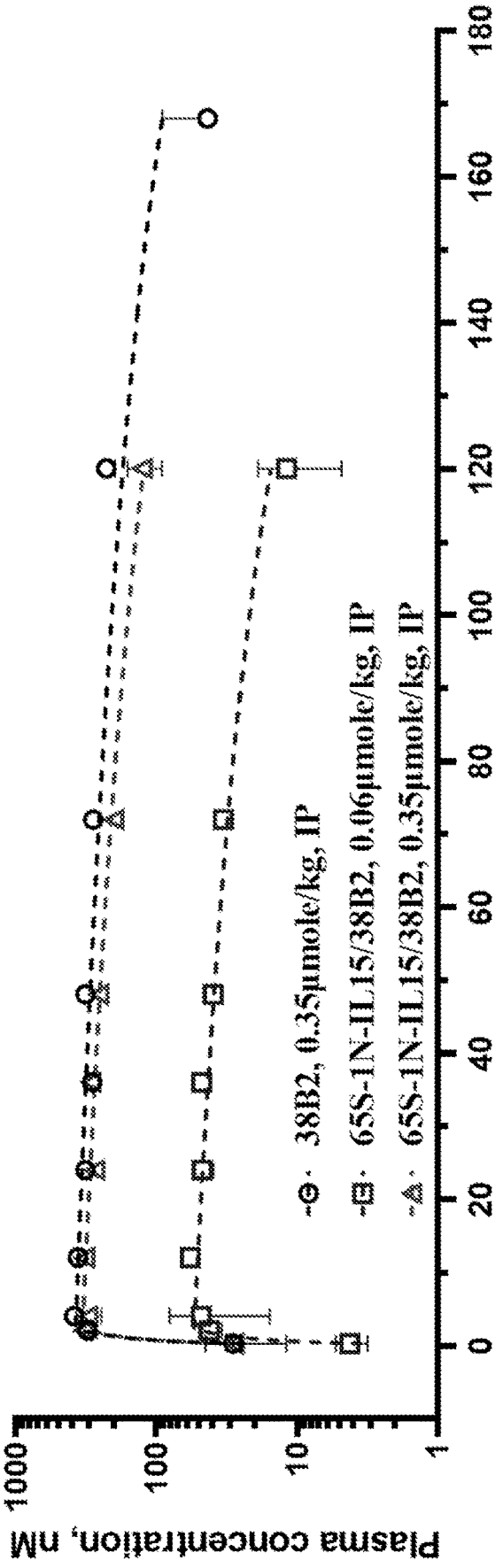

Plasma concentration, nM
1000
100
10
1
0
20
40
60
80
100
120
140
160
180
Time (h)
38B2, 0.35µmole/kg, IP
65S-1N-IL15/38B2, 0.06µmole/kg, IP
65S-1N-IL15/38B2, 0.35µmole/kg, IP

Fig. 36B

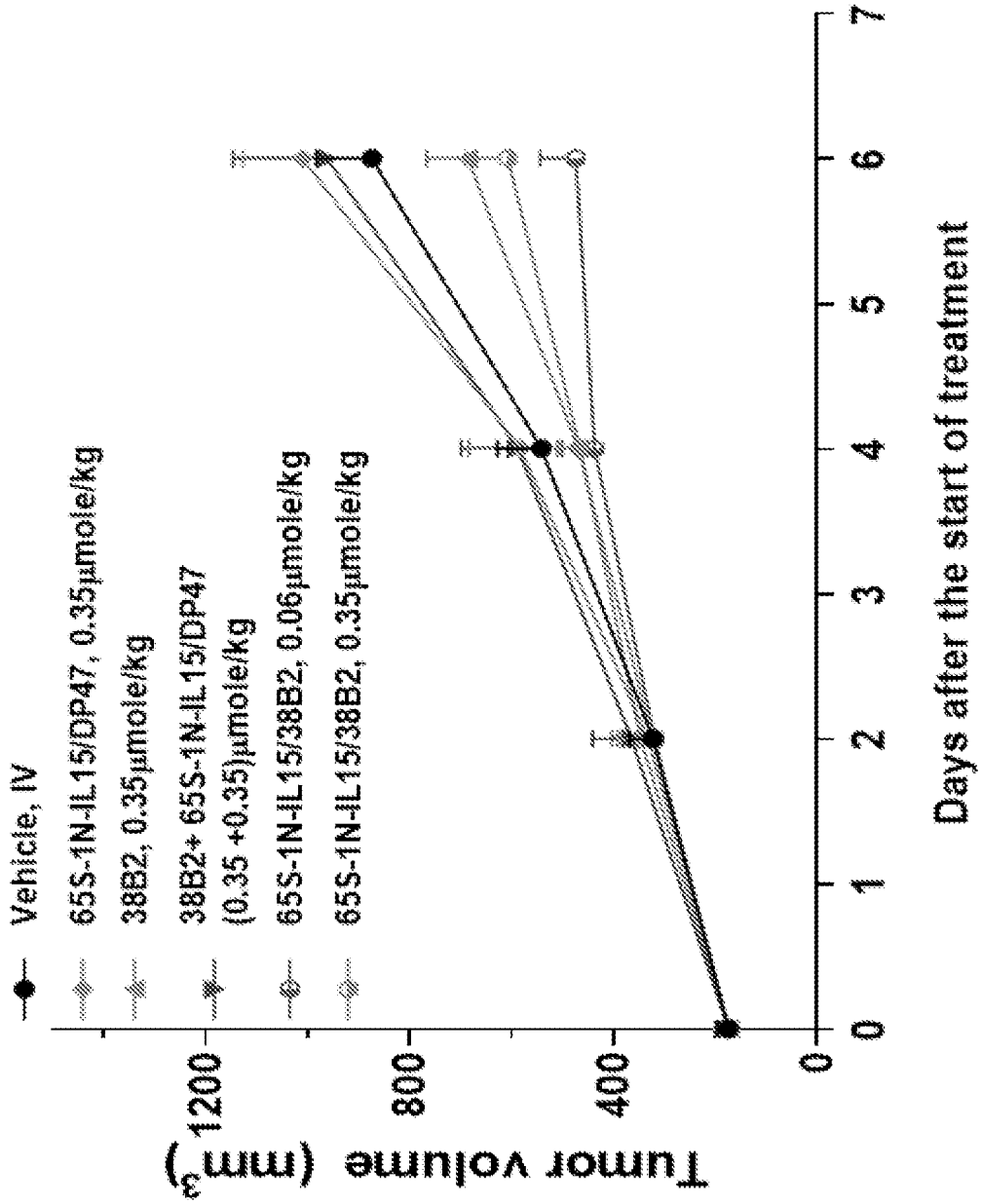
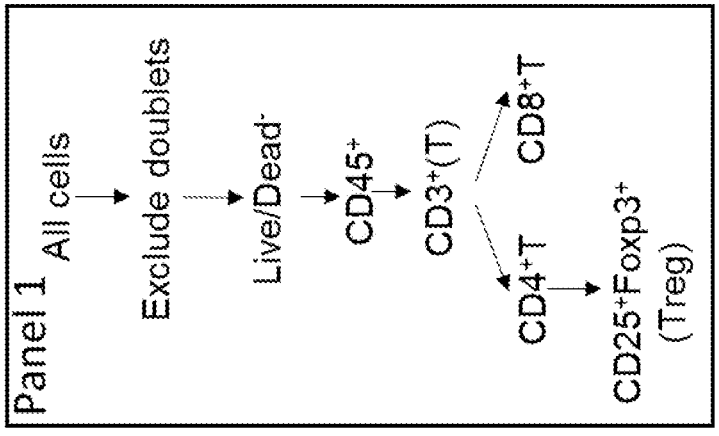

Vehicle, IV
65S-1N-IL15/DP47, 0.35µmole/kg
38B2, 0.35µmole/kg
38B2+ 65S-1N-IL15/DP47 (0.35 +0.35)µmole/kg
65S-1N-IL15/38B2, 0.06µmole/kg
65S-1N-IL15/38B2, 0.35µmole/kg
Tumor volume (mm³)
1200
800
400
0
0
1
2
3
4
5
6
7
Days after the start of treatment

Fig. 37A


Panel 1
All cells
Exclude doublets
Live/Dead-
CD45+
CD3+(T)
CD4+T
CD8+T
CD25+Foxp3+
(Treg)

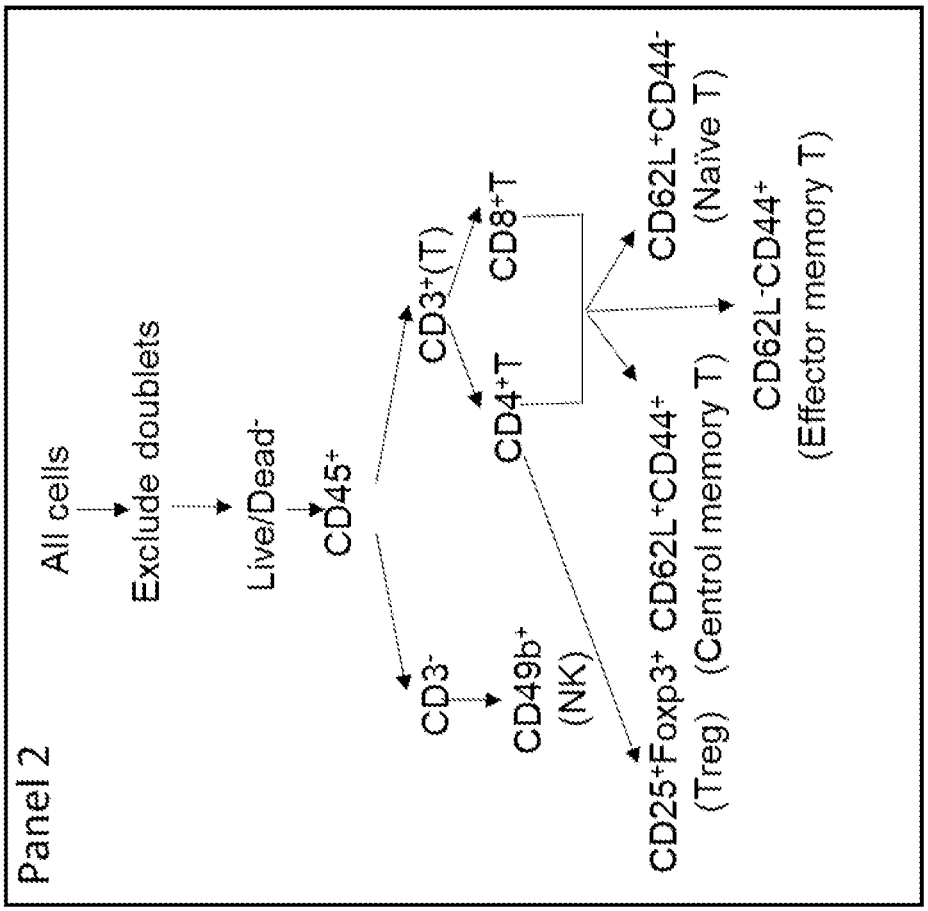

Panel 2
All cells
Exclude doublets
Live/Dead-
CD45+
CD3+(T)
CD4+T
CD8+T
CD3-
CD49b+
(NK)
CD25+Foxp3+ CD62L+CD44+
(Treg) (Control memory T)
CD62L+CD44-
(Naïve T)
CD62L-CD44+
(Effector memory T)

Fig. 37B

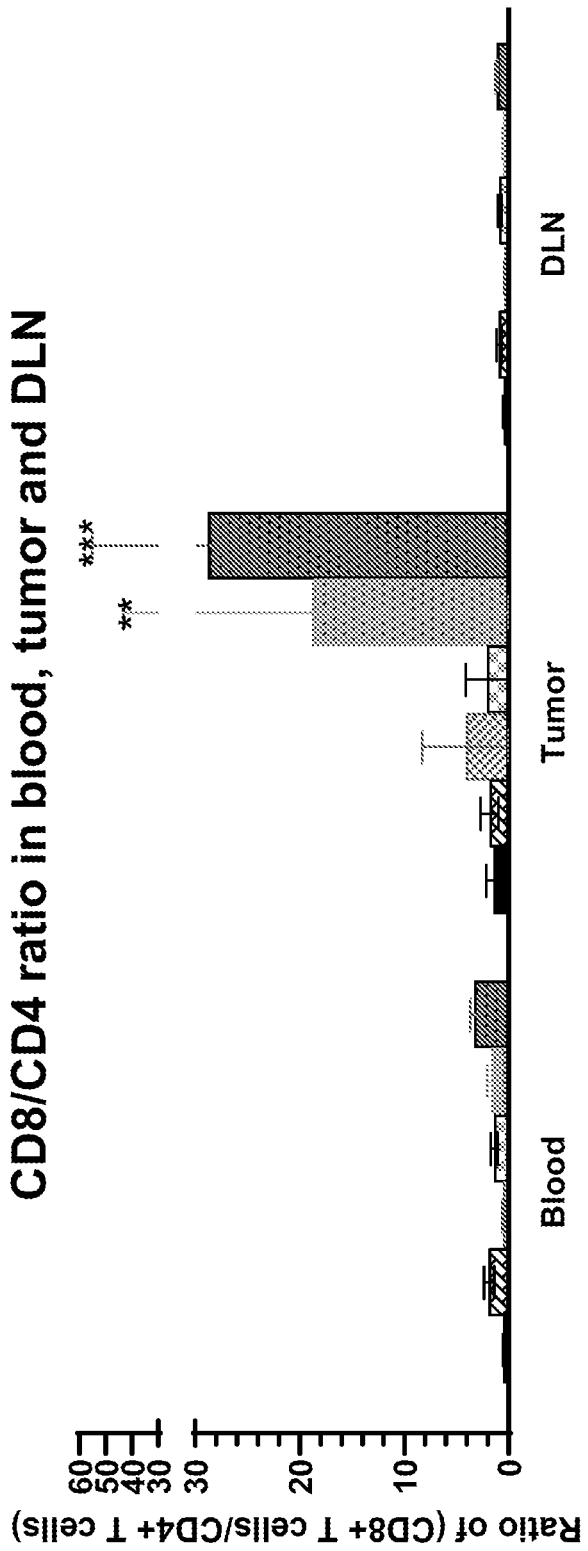

CD8/CD4 ratio in blood, tumor and DLN
Ratio of (CD8+ T cells/CD4+ T cells)
60
50
40
30
20
10
0
***
**
Blood
Tumor
DLN
Vehicle
65S-1N-IL15/DP47 (0.35µmole/kg)
38B2 (0.35µmole/kg)
38B2+65S-1N-IL15/DP47 (0.35µmole/kg each)
65S-1N-IL15/38B2(0.06µmole/kg)
65S-1N-IL15/38B2 (0.35µmole/kg)

Fig. 37C

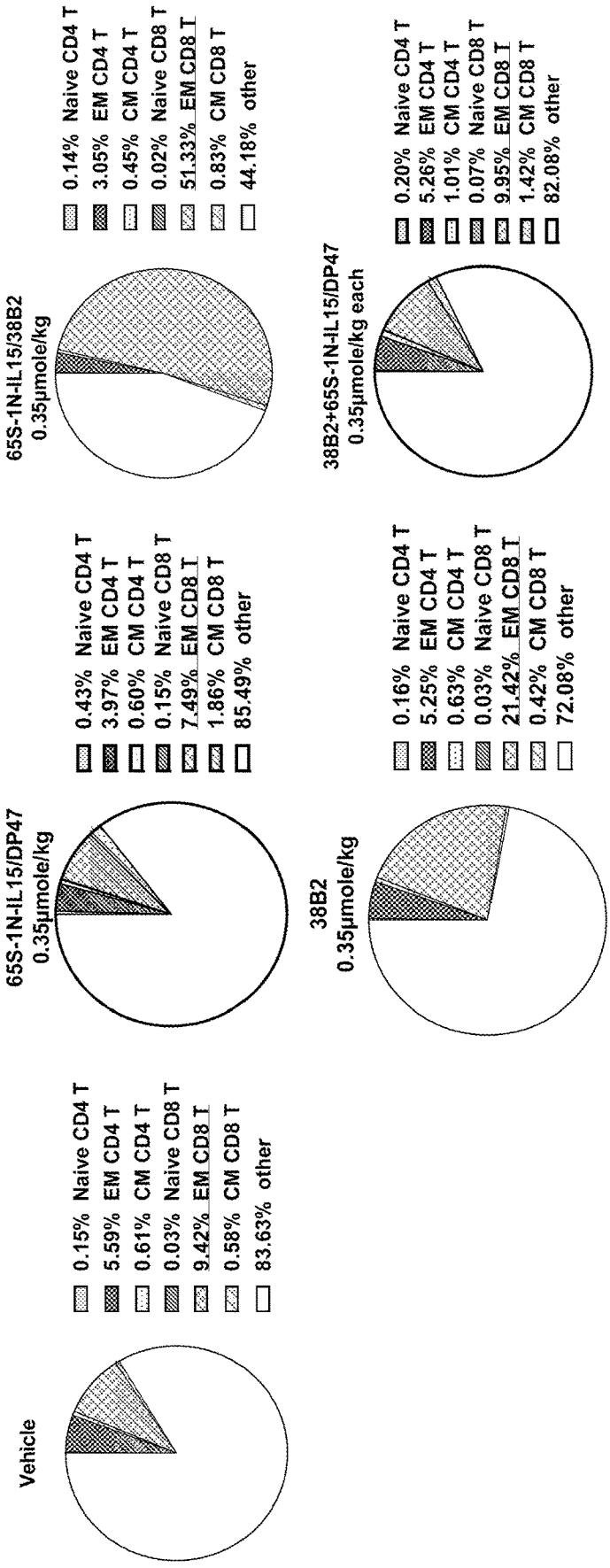

Vehicle
0.15% Naive CD4 T
5.59% EM CD4 T
0.61% CM CD4 T
0.03% Naive CD8 T
9.42% EM CD8 T
0.58% CM CD8 T
83.63% other
65S-1N-IL15/DP47
0.35µmole/kg
0.43% Naive CD4 T
3.97% EM CD4 T
0.60% CM CD4 T
0.15% Naive CD8 T
7.49% EM CD8 T
1.86% CM CD8 T
85.49% other
38B2
0.35µmole/kg
0.16% Naive CD4 T
5.25% EM CD4 T
0.63% CM CD4 T
0.03% Naive CD8 T
21.42% EM CD8 T
0.42% CM CD8 T
72.08% other
65S-1N-IL15/38B2
0.35µmole/kg
0.14% Naive CD4 T
3.05% EM CD4 T
0.45% CM CD4 T
0.02% Naive CD8 T
51.33% EM CD8 T
0.83% CM CD8 T
44.18% other
38B2+65S-1N-IL15/DP47
0.35µmole/kg each
0.20% Naive CD4 T
5.26% EM CD4 T
1.01% CM CD4 T
0.07% Naive CD8 T
9.95% EM CD8 T
1.42% CM CD8 T
82.08% other

Fig. 37D

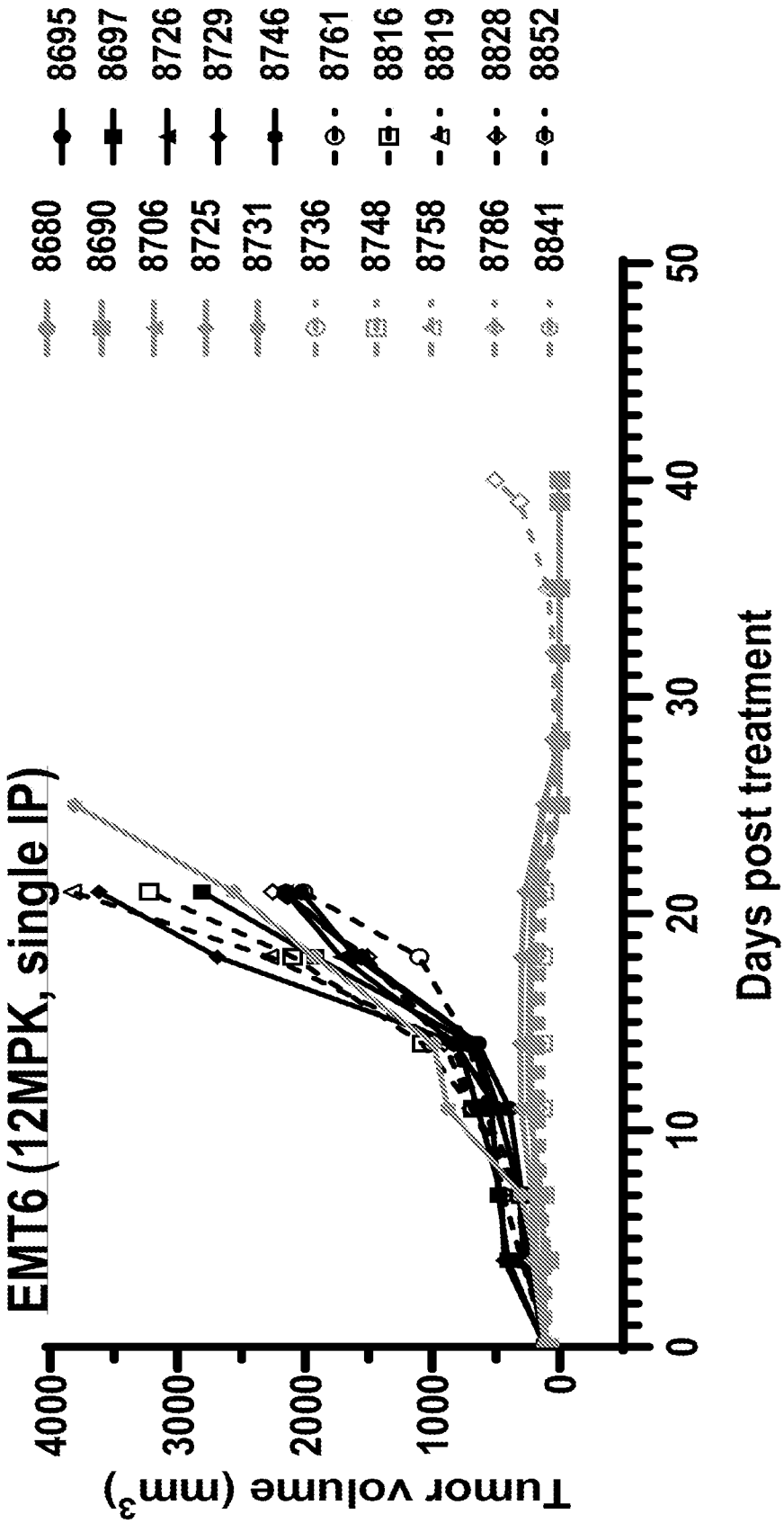

EMT6 (12MPK, single IP)
Tumor volume (mm3)
4000
3000
2000
1000
0
0
10
20
30
40
50
Days post treatment
8680
8690
8706
8725
8731
8736
8748
8758
8786
8841
8695
8697
8726
8729
8746
8761
8816
8819
8828
8852

Fig. 38

ANTI-PD-1 ANTIBODIES AND FUSION PROTEINS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application is a national phase entry pursuant to 35 U.S.C. § 371 of International Application No. PCT/US2021/038740, filed Jun. 23, 2021, which claims the benefit of priority to U.S. Provisional Patent Application No. 63/043,114, filed Jun. 23, 2020, and to U.S. Provisional Patent Application No. 63/111,459, filed Nov. 9, 2020, which are incorporated by reference herein in their entireties.

SEQUENCE LISTING

[0002] The present application contains a Sequence Listing which has been submitted in txt format. Said txt copy, created Jun. 28, 2023, is named "2023-06-28_01183-0208-00US-KAD_ST25_ST25" and is 435,942 bytes in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

FIELD

[0003] The present disclosure relates generally to the field of molecular biology and medicine. More particularly, the disclosure provides fusion proteins comprising an anti-PD-1 antibody or antigen-binding fragment thereof linked to an IL-15 polypeptide, which in turn is linked to an IL-15 receptor alpha (IL-15Rα) polypeptide comprising the IL-15Rα sushi domain. In addition, the disclosure provides antibodies, and antigen-binding fragments thereof, that specifically bind to PD-1 as well as fusion proteins comprising such anti-PD-1 antibodies and PD-1 binding fragments thereof. Also disclosed are therapeutic compositions comprising the antibody fusions or antibodies for treating disease.

BACKGROUND

[0004] PD-1 is a 55 KD type I transmembrane protein of 286 amino acids, which contains a membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal tyrosine-based switch motif (ITSM). The PD-1 cytosolic domain contains two tyrosines, with the closest tyrosine (VAYEEL in mouse PD-1) located within the ITIM. The human PD-1 protein and the murine PD-1 protein share about 60% amino acid identity, with four potential N-glycosylation sites and residues that define the Ig-V domain are conserved. ITIM-like motifs surrounding the ITIM and C-terminal tyrosine in the cytoplasmic region are also conserved between human orthologue and murine orthologue. PD-1 is a member of CD-28 family of receptors, which is primarily expressed on mature T cells in peripheral tissues and the tumor microenvironment. PD-1 is also expressed on other non-T cell subsets including B cells, professional antigen presenting cells (APCs), and natural killer (NK) cells.

[0005] The ligands for PD-1 are the B7 family members PD-L1 (also known as B7-H1 and CD274) and PD-L2 (also known as B7-DC and CD273). PD-L1 is expressed primarily on both lymphoid and non-lymphoid tissues such as CD4 and CD8 T cells, macrophage lineage cells, peripheral tissues as well as on tumor cells, virally infected cells and autoimmune tissue cells. However, PD-L2 has a more restricted expression than PD-L1, being expressed only on macrophages and activated dendritic cells. PD-1 ligands are expressed in many human cancers, including melanoma, glioma, non-small cell lung cancer, squamous cell carcinoma of head and neck, leukemia, pancreatic cancer, renal cell carcinoma, and hepatocellular carcinoma, and may be inducible in nearly all cancer. Interaction between PD-1 and its ligands results in dephosphorylation and inactivation of the T cell kinase ZAP70, and the recruitment of SHP2. SHP2 directly dephosphorylates PI3K, which inhibits downstream activation of Aktin causing a decrease in tumor infiltrating lymphocytes, and a decrease in T cell receptor mediated proliferation, leading to immune evasion. Inhibiting interaction between PD-1 and PD-L1 reverses immune suppression and the effect may be additive when the interaction of PD-1 with PD-L2 is blocked as well.

[0006] Several commercial anti-PD-1 antibodies are currently used to treat diseases that involve PD-1-mediated immune suppression. However, only a subset of patients responds well to these therapies. Depending on the indication and other factors, the typical response rate of patients for each monotherapy ranges from 10% to 30%. One possible reason for this lack of response could be the absence of an inflammatory tumor microenvironment (TME), including activated anti-tumor $CD8^+$ and $CD4^+$ T cells as well as other effectors such as NK cells.

[0007] Combination therapies involving PD-1 antibodies with various cytokines such as IL-2, IL-15, IL-21, tumor necrosis factor (TNF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) may have some efficacy in treating cancer and infection. However, these therapies are limited by the systemic toxicity that is associated both with the high blood concentrations of cytokines that is required to obtain efficacy and with the lack of specificity of the administered cytokine for affected cells and tissues.

[0008] IL-15 is a 12.5 KD glycoprotein with 114 amino acids and belongs to the four α-helix bundle family of cytokines that also includes IL-2, IL-4, IL-7, IL-9, granulocyte colony-stimulating factor (G-CSF), and GM-CSF. IL-15 is secreted by macrophages, dendritic cells, and monocytes. IL-15 can stimulate central memory CD8 cells to exert immunity without modulating effects on other T cells. Additionally, IL-15 can activate NK cells and effector and memory CD8 T cells and can rescue T cells from apoptosis induced by regulatory T cells (Tregs). Administration of IL-15 is also associated with a lower risk of inducing systemic toxicity at a higher dose compared to other cytokines. Human IL-15 can be soluble or membrane-bound. The membrane-bound I1-15, which is the major form of IL-15, is either formed by binding of IL-15 to cellular membrane directly or by presentation of IL-15 by the membrane-bound IL-15R receptor.

[0009] The I1-15 receptor is composed of three subunits: IL-15Rα, IL-15R, and IL-15Rγ. IL-15 typically forms a complex with IL-15 receptor α expressed on APCs prior to binding to functional IL-15Rβ and γ units on T cells and NK cells. IL-15 can bind to IL-15Rα receptor alone with affinity (K_a=1.1011 M^{-1}). It can also bind to IL-15Rβγc signaling complex with lower affinity (K_a=1.109 M^{-1}). The sushi domain (29.5 KD) of the IL-15Rα plays a critical role in complex formation of IL-15 and IL-15Rα.

[0010] One of the limitations with systemic IL-15 treatment is its very short half-life in vivo. Therefore, there is a need to generate a suitable immune-stimulatory form of

IL-15/IL-15Rα that has a longer half-life in vivo while retaining its ability to medulate the immune response. Additionally, there is a need for effective IL-15 antagonists that can be selectively targeted to the disease site to avoid unwanted systemic toxicities and provide a more effective therapeutic benefit.

[0011] Compounds that modulate PD-1 activity have potential as therapeutic agents for the treatment of various diseases and disorders, including cancer, inflammation, and autoimmune diseases. There is a significant unmet need to develop new strategies to target various effector molecules to a disease site to provide therapeutic benefit without the side effects associated with non-specific immune activity.

SUMMARY

[0012] Provided herein are fusion proteins, antibodies, and antigen-binding fragments thereof that bind to PD-1. In embodiments, the fusion proteins comprise an anti-PD-1 antibody, or antigen-binding fragment thereof. Also disclosed are anti-PD-1 antibodies and the antigen-binding fragments thereof that bind PD-1. Also provided are therapeutic compositions of such fusion proteins, antibodies, and antigen-binding fragments thereof, as well as methods of using these fusion proteins, antibodies and antigen-binding fragments thereof.

[0013] In one aspect, the disclosure provides a fusion protein comprising a PD-1 binding protein, an IL-15 receptor (IL-15R) binding protein (e.g., IL-15 or an IL-15R binding portion thereof), and an IL-15 binding protein (e.g., IL-15Rα or an IL-15 binding portion thereof comprising the IL-15Rα sushi domain). In one aspect, the PD-1 binding protein is an antibody or PD-1 binding fragment thereof. In one embodiment, the IL-15 receptor-binding portion is IL-15. In embodiments, IL-15 is joined, directly or indirectly, to the sushi domain of IL-15Rα.

[0014] In one embodiment, the fusion protein comprises an anti-PD-1 antibody and an IL-15 polypeptide, wherein the C-terminus of the IL-15 polypeptide is covalently linked, directly or via a polypeptide linker, to the N-terminus of the heavy chain variable region of one of the antibody heavy chains (i.e., the antibody heavy chains form a heterodimer wherein one of the heavy chains is linked to an IL-15 polypeptide. In one embodiment, the N-terminus of the IL-15 polypeptide is linked to the C-terminus of an IL-15Rα sushi domain polypeptide.

[0015] In one embodiment, the fusion protein comprises an anti PD-1 antibody and two IL-15 polypeptides, wherein each IL-15 polypeptide is covalently linked to the N-terminus of an antibody heavy chain.

[0016] In embodiments in which only one heavy chain is linked to IL-15/IL-15Rα sushi domain, the Fc domains of the antibody may comprise one or more amino acid substitutions promoting heterodimer formation (i.e., the association of a heavy chain fusion with a heavy chain lacking the fusion). In embodiments, an amino acid residue in the CH3 domain of one heavy chain (CH3-1) comprises an amino acid substitution replacing an amino acid with an amino acid residue having a larger side chain volume, thereby generating a "knob" within the CH3 domain, which is positionable in a "hole" present within the CH3 domain of the other heavy chain (CH3-2), generated by replacing an amino acid residue with an amino acid residue having a smaller side chain volume. In embodiments, the amino acid substitutions are selected from the following groups:

[0017] (1) CH3 domain of first heavy chain: S354C, T366W; CH3 domain of second heavy chain: Y349C, T366S, L368A, Y407V

[0018] (2) CH3 domain of first heavy chain: T350V, L351Y, F405A, Y407V; CH3 domain of second heavy chain: T350V, T366L, K392L, T394W

[0019] (3) CH3 domain of first heavy chain: L351Y, F405A, Y407V; CH3 domain of second heavy chain: T366L, K392L, T394W.

[0020] Either the first or second heavy chain may be linked to the IL-15/IL-15Rα sushi domain.

[0021] In embodiments, the IL-15Rα polypeptide and the IL-15 polypeptide are joined by a first linker. In embodiments, the IL-15 polypeptide and the anti-PD-1 antibody, or antigen-binding portion thereof, are joined by a second linker. In embodiments, the length of the linker may independently be between 10 to 40 amino acids. In embodiments, the length of the linker is 25 to 35 amino acids. In embodiments, the linker sequences comprises near neutral amino acids selected from the group comprising Gly (G), Asn (N), Ser (S), Thr (T), Ala (A), Leu (L), and Gln (Q), most preferably in the group comprising Gly (G), Asn (N), and Ser (S). In certain embodiments, the linker sequences are glycine and serine rich, and in some embodiments, the linker contains only serine and glycine residues.

[0022] In certain embodiments, the IL-15 and/or the IL-15Rα sushi domain comprise one or more amino acid substitutions. In embodiments, the amino acid substitutions are located at position 1, 4, 8, 30, 45, 61, 64, 65, and/or 108 of IL-15. In some embodiments, the amino acid substitutions are located at positions 45, 65, and/or 108 of IL-15. In some embodiments the amino acid substitutions are one or more of N1D, N4D, D8N, D30N, D61N, E64Q, L45A, N65S/A/D/K, and/or Q108S/E substitutions in IL-15. In some embodiments, the amino acid substitutions are L45A, N65S/A/D/K, and/or Q108S substitutions in IL-15. In one embodiment, the amino acid substitution is an N65S substitution in IL-15.

[0023] In one embodiment, the amino acid substitution is an N60 substitution in the IL-15Rα sushi domain. In one embodiment, the amino acid substitution is an N60A substitution in the IL-15Rα sushi domain.

[0024] In embodiments, the fusion protein comprises an IL-15 polypeptide comprising one of the following amino acid substitutions: N65S, N65A, or N65D. In embodiments, the fusion protein comprises an IL-15 polypeptide comprising one or more of the following amino acid substitutions: (1) L45A, (2) N65S, N65A, or N65D, and (3) Q108S. In one embodiment, the fusion protein comprises an IL-15Rα sushi domain polypeptide comprisings an N60A amino acid substitution.

[0025] In one aspect, the disclosure relates to a fusion protein comprising:

[0026] (i) an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprise a CDR1, CDR2, and CDR3;

[0027] (ii) an IL-15 polypeptide or derivative thereof;

[0028] (iii) an IL-15Rα sushi domain polypeptide or derivative thereof; and

[0029] (iv) a linker polypeptide joining the IL-15Rα sushi domain polypeptide and the IL-15 polypeptide or derivative thereof.

[0030] In one aspect, the disclosure relates to a fusion protein comprising:

[0031] (i) an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprise a CDR1, CDR2, and CDR3;

[0032] (ii) an IL-15 polypeptide comprising the amino acid sequence of SEQ ID NO: 212, or an amino acid sequence that is at least 90% or at least 95% identical to SEQ ID NO: 212;

[0033] (iii) an IL-15Rα sushi domain polypeptide comprising the amino acid sequence of SEQ ID NO: 214, or an amino acid sequence that is at least 95% identical to SEQ ID NO: 214; and

[0034] (iv) a first linker polypeptide joining the IL-15Rα sushi domain polypeptide and the IL-15 polypeptide.

[0035] The anti-PD-1 antibody, or antigen-binding fragment thereof, portion of the fusion protein can be any antibody, or antigen-binding fragment thereof, that specifically binds PD-1, including those comprising the corresponding heavy and light chain variable regions and/or CDRs provided in FIG. **1**, or otherwise described herein. In embodiments, the fusion protein comprises an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein the CDRs of the heavy and light chain variable regions comprise the following sequences:

[0036] the sequence of CDR1 of the heavy chain variable region (CDR1H) comprises the sequence of SEQ ID NO: 21;

[0037] the sequence of CDR2 of the heavy chain variable region (CDR2H) comprises the sequence of SEQ ID NO: 22;

[0038] the sequence of CDR2 of the heavy chain variable region (CDR3H) comprises the sequence of SEQ ID NO: 23;

[0039] the sequence of CDR1 of the light chain variable region (CDR1L) comprises the sequence $RX_{13}X_{14}X_{15}X_{16}IX_{17}X_{18}WX_{19}X_{20}$ (SEQ ID NO:135);

[0040] wherein X_{13} is A or V;

[0041] wherein X_{14} is S or G;

[0042] wherein X_{15} is Q, E, or R;

[0043] wherein X_{16} is G, S, D or N;

[0044] wherein X_{17} is G, S, or N;

[0045] wherein X_{18} is S, I, R, T, K, P, N, H, or V;

[0046] wherein X_{19} is L or V; and

[0047] wherein X_{20} is G or A; and

[0048] the sequence of CDR2 of the light chain variable region (CDR2L) comprises the sequence $X_{21}AX_{22}X_{23}X_{24}X_{23}X_{26}$ (SEQ ID NO: 136); and

[0049] wherein X_{21} is S, D, E, or A;

[0050] wherein X_{22} is S or K;

[0051] wherein X_{23} is S, N, T, R, or D;

[0052] wherein X_{24} is L or V;

[0053] wherein X_{25} is Q, E, or H; and

[0054] wherein X_{26} is S, N, A, R, P, or T; and

[0055] the sequence of CDR3 of the light chain variable region (CDR3L) comprises the sequence $QQX_{27}X_{28}SFPX_{29}X_{30}$ (SEQ ID NO: 137);

[0056] wherein X_{27} is A or G;

[0057] wherein X_{28} is N, D, or Y;

[0058] wherein X_{29} is F or L; and

[0059] wherein X_{30} is A or T.

[0060] In embodiments, the fusion protein comprises an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein the CDRs of the heavy and light chain variable regions comprise the following sequences:

[0061] the sequence of CDR1H comprises the sequence of SEQ ID NO: 21;

[0062] the sequence of CDR2H comprises the sequence of SEQ ID NO: 22;

[0063] the sequence of CDR3H comprises the sequence of SEQ ID NO: 23

[0064] the sequence of CDR1L comprises the sequence of SEQ ID NO: 96;

[0065] the sequence of CDR2L comprises the sequence of SEQ ID NO: 97; and

[0066] the sequence of CDR3L comprises the sequence of SEQ ID NO: 82.

[0067] In embodiments, the fusion protein comprises an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein:

[0068] the heavy chain variable region comprises SEQ ID NO: 24, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 24; and

[0069] the light chain variable region comprises SEQ ID NO: 98, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 98.

[0070] In embodiments, the fusion protein comprises an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein the CDRs of the heavy chain and light chain variable regions comprise the following sequences:

[0071] the sequences of CDR1H, CDR2H and CDR3H comprise respectively SEQ ID NOS: 21, 22, and 23; and

[0072] the sequences of CDR1L, CDR2L and CDR3L comprise respectively, SEQ ID NOS: 45, 46, and 47; SEQ ID NOS: 66, 67, and 68; SEQ ID NOS: 70, 67, and 71; SEQ ID NOS: 73, 74, and 75; SEQ ID NOS: 77, 78, and 47; SEQ ID NOS: 80, 81, and 82; SEQ ID NOS: 77, 78, and 84; SEQ ID NOS: 77, 86, and 47; SEQ ID NOS: 88, 89, and 47; SEQ ID NOS: 66, 67, and 47; SEQ ID NOS: 80, 92, and 75; SEQ ID NOS: 80, 94, and 71; SEQ ID NOS: 99, 100, and 47; SEQ ID NOS: 102, 103, and 104; SEQ ID NOS: 106, 103, and 47; SEQ ID NOS: 108, 103, and 47; SEQ ID NOS: 110, 111, and 75; SEQ ID NOS: 77, 103, and 113; SEQ ID NOS: 77, 111, and 47; SEQ ID NOS: 116, 67, and 47; SEQ ID NOS: 118, 119, and 47; SEQ ID NOS: 80, 78, and 47; SEQ ID NOS: 122, 103 and 47; SEQ ID NOS: 124, 125, and 75; SEQ ID NOS: 127, 38, and 68; SEQ ID NOS: 129, 130, and 47; or SEQ ID NOS: 132, 133, and 75.

[0073] In embodiments, the fusion protein comprises an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein:

[0074] the heavy chain variable region comprises SEQ ID NO: 24, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 24; and

[0075] the light chain variable region comprises SEQ ID NO: 48, 69, 72, 76, 79, 83, 85, 87, 90, 91, 93, 95, 101, 105, 107, 109, 112, 114, 115, 117, 120, 121, 123, 126, 128, 131, or 134, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any of SEQ ID NO: 48, 69, 72, 76, 79, 83, 85, 87, 90, 91, 93, 95, 101, 105, 107, 109, 112, 114, 115, 117, 120, 121, 123, 126, 128, 131, or 134.

[0076] In embodiments, the fusion protein comprises an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein the CDRs of the heavy and light chain variable regions comprise the following sequences:

[0077] the sequence of CDR1H comprises the sequence of SEQ ID NO: 17;

[0078] the sequence of CDR2H comprises the sequence of SEQ ID NO: 18;

[0079] the sequence of CDR3H comprises the sequence of SEQ ID NO: 19;

[0080] the sequence of CDR1L comprises the sequence $RSSX_1SLLX_2SNGX_3X_4YLD$ (SEQ ID NO:62),

[0081] wherein X_1 is Q or E;

[0082] wherein X_2 is H or Y;

[0083] wherein X_3 is Y or N; and

[0084] wherein X_4 is T or N;

[0085] the sequence of CDR2L comprises the sequence $X_5X_6SX_7X_8X_9X_{10}$ (SEQ ID NO: 63),

[0086] wherein X_5 is L, Q or E;

[0087] wherein X_6 is S, A, or V;

[0088] wherein X_7 is H, N, T, or S;

[0089] wherein X_8 is R or L;

[0090] wherein X_9 is G, A, or H; and

[0091] wherein X_{10} is S or T; and

[0092] the sequence of CDR3L comprises the sequence $MQGX_{11}X_{12}WPYT$ (SEQ ID NO: 64),

[0093] wherein X_{11} is A, T, or S; and

[0094] wherein X_{12} is H or R.

[0095] In embodiments, the fusion protein comprises an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein the CDRs of the heavy chain and light chain variable regions comprise the following sequences:

[0096] the sequence of CDR1H comprise the sequence of SEQ ID NO: 17;

[0097] the sequence of CDR2H comprises the sequence of SEQ ID NO: 18;

[0098] the sequence of CDR3H comprises the sequence of SEQ ID NO: 19;

[0099] the sequence of CDR1L comprises the sequence of SEQ ID NO: 41;

[0100] the sequence of CDR2L comprises the sequence of SEQ ID NO: 49; and

[0101] the sequence of CDR3 of the light chain variable region (CDR3L) comprises the sequence of SEQ ID NO: 50.

[0102] In embodiments, the fusion protein comprises an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein:

[0103] the heavy chain variable region comprises SEQ ID NO: 20, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 20; and

[0104] the light chain variable region comprises SEQ ID NO: 51, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 51.

[0105] In embodiments, the fusion protein comprises an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein the CDRs of the heavy chain and light chain variable regions comprise the following sequences:

[0106] the sequence of CDR1H, CDR2H and CDR3H comprise SEQ ID NOS: 17, 18, and 19, respectively; and

[0107] the sequence of CDR1L, CDR2L and CDR3L comprise respectively, SEQ ID NOS: 41, 42, and 43; SEQ ID NOS: 41, 52, and 53; SEQ ID NOS: 41, 55, and 56; or SEQ ID NOS: 58, 59, and 60.

[0108] In further embodiments the fusion protein comprises an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein:

[0109] the heavy chain variable region comprises SEQ ID NO: 20, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 20; and

[0110] the light chain variable region comprises SEQ ID NO: 44, 54, 57, or 61, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NO: 44, 54, 57, or 61.

[0111] In another aspect the disclosure provides an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof binds to PD-1, and wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region wherein each of the heavy chain and the light chain variable regions comprise a CDR1, CDR2, and CDR3 and wherein the antibody heavy chains comprise a constant region comprising three constant domains CH1, CH2, and CH3.

[0112] In embodiments, the CDRs of the anti-PD-1 antibody, or antigen-binding fragment thereof, comprise the following sequences:

[0113] the sequence of CDR1H comprises the sequence of SEQ ID NO: 21;

[0114] the sequence of CDR2H comprises the sequence of SEQ ID NO: 22;

[0115] the sequence of CDR3H comprises the sequence of SEQ ID NO: 23;

[0116] the sequence of CDR1L comprises the sequence $RX_{13}X_{14}X_{15}X_{16}IX_{17}X_{18}WX_{19}X_{20}$ (SEQ ID NO:135);

[0117] wherein X_{13} is A or V;

[0118] wherein X_{14} is S or G;

[0119] wherein X_{15} is Q, E, or R;

[0120] wherein X_{16} is G, S, D or N;

[0121] wherein X_{17} is G, S, or N;

[0122] wherein X_{18} is S, I, R, T, K, P, N, H, or V;

[0123] wherein X_{19} is L or V;

[0124] wherein X_{20} is G or A; and

[0125] the sequence of CDR2L comprises the sequence $X_{21}AX_{22}X_{23}X_{24}X_{23}X_{26}$ (SEQ ID NO: 136); and

[0126] wherein X_{21} is S, D, E, or A;

[0127] wherein X_{22} is S or K;

[0128] wherein X_{23} is S, N, T, R, or D;

[0129] wherein X_{24} is L or V;

[0130] wherein X_{25} is Q, E, or H; and

[0131] wherein X_{26} is S, N, A, R, P, or T; and

[0132] the sequence of CDR3L comprises the sequence $QQX_{27}X_{28}SFPX_{29}X_{30}$ (SEQ ID NO: 137);

[0133] wherein X_{27} is A or G;

[0134] wherein X_{28} is N, D, or Y;

[0135] wherein X_{29} is F or L; and

[0136] wherein X_{30} is A or T.

[0137] In embodiments, the CDRs of the anti-PD-1 antibody, or antigen-binding fragment thereof, comprise the following sequences:

[0138] the sequence of CDR1H comprises the sequence of SEQ ID NO: 21;

[0139] the sequence of CDR2H comprises the sequence of SEQ ID NO: 22;

[0140] the sequence of CDR3H comprises the sequence of SEQ ID NO: 23

[0141] the sequence of CDR1L comprises the sequence of SEQ ID NO: 96;

[0142] the sequence of CDR2L comprises the sequence of SEQ ID NO: 97; and

[0143] the sequence of CDR3L comprises the sequence of SEQ ID NO: 82.

[0144] In embodiments, the anti-PD-1 antibody, or antigen-binding fragment thereof, comprises:

[0145] a heavy chain variable region comprising SEQ ID NO: 24, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 24; and

[0146] a light chain variable region comprising SEQ ID NO: 98, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 98.

[0147] In embodiments, the CDRs of the anti-PD-1 antibody, or antigen-binding fragment thereof, comprise the following sequences:

[0148] the sequences of CDR1H, CDR2H and CDR3H comprise respectively SEQ ID NOS: 21, 22, and 23; and

[0149] the sequences of CDR1L, CDR2L and CDR3L comprise respectively, SEQ ID NOS: 45, 46, and 47; SEQ ID NOS: 66, 67, and 68; SEQ ID NOS: 70, 67, and 71; SEQ ID NOS: 73, 74, and 75; SEQ ID NOS: 77, 78, and 47; SEQ ID NOS: 80, 81, and 82; SEQ ID NOS: 77, 78, and 84; SEQ ID NOS: 77, 86, and 47; SEQ ID NOS: 88, 89, and 47; SEQ ID NOS: 66, 67, and 47; SEQ ID NOS: 80, 92, and 75; SEQ ID NOS: 80, 94, and 71; SEQ ID NOS: 99, 100, and 47; SEQ ID NOS: 102, 103, and 104; SEQ ID NOS: 106, 103, and 47; SEQ ID NOS: 108, 103, and 47; SEQ ID NOS: 110, 111, and 75; SEQ ID NOS: 77, 103, and 113; SEQ ID NOS: 77, 111, and 47; SEQ ID NOS: 116, 67, and 47; SEQ ID NOS: 118, 119, and 47; SEQ ID NOS: 80, 78, and 47; SEQ ID NOS: 122, 103 and 47; SEQ ID NOS: 124, 125, and 75; SEQ ID NOS: 127, 38, and 68; SEQ ID NOS: 129, 130, and 47; or SEQ ID NOS: 132, 133, and 75.

[0150] In embodiments, the anti-PD-1 antibody, or antigen-binding fragment thereof, comprises:

[0151] a heavy chain variable region comprising SEQ ID NO: 24, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 24; and

[0152] a light chain variable region comprising SEQ ID NO: 48, 69, 72, 76, 79, 83, 85, 90, 91, 93, 101, 105, 107, 109, 112, 114, 115, 117, 120, 121, 123, 126, 128, 131, or 134, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NO: 48, 69, 72, 76, 79, 83, 85, 90, 91, 93, 101, 105, 107, 109, 112, 114, 115, 117, 120, 121, 123, 126, 128, 131, or 134.

[0153] In embodiments, the CDRs of the anti-PD-1 antibody, or antigen-binding fragment thereof, comprise the following sequences:

[0154] the sequence of CDR1H comprises the sequence of SEQ ID NO: 17;

[0155] the sequence of CDR2H comprises the sequence of SEQ ID NO: 18;

[0156] the sequence of CDR3H comprises the sequence of SEQ ID NO: 19;

[0157] the sequence of CDR1L comprises the sequence $RSSX_1SLLX_2SNGX_3X_4YLD$ (SEQ ID NO:62),

[0158] wherein X_1 is Q or E;

[0159] wherein X_2 is H or Y;

[0160] wherein X_3 is Y or N; and

[0161] wherein X_4 is T or N;

[0162] the sequence of CDR2L comprises the sequence $X_5X_6SX_7X_8X_9X_{10}$ (SEQ ID NO: 63),

[0163] wherein X_5 is L, Q or E;

[0164] wherein X_6 is S, A, or V;

[0165] wherein X_7 is H, N, T, or S;

[0166] wherein X_8 is R or L;

[0167] wherein X_9 is G, A, or H; and

[0168] wherein X_{10} is S or T; and

[0169] the sequence of CDR3L comprises the sequence $MQGX_{11}X_{12}WPYT$ (SEQ ID NO: 64),

[0170] wherein X_{11} is A, T, or S; and

[0171] wherein X_{12} is H or R.

[0172] In embodiments, the CDRs of the anti-PD-1 antibody, or antigen-binding fragment thereof, comprise the following sequences:

[0173] the sequence of CDR1H comprises the sequence of SEQ ID NO: 17;

[0174] the sequence of CDR2H comprises the sequence of SEQ ID NO: 18;

[0175] the sequence of CDR3H comprises the sequence of SEQ ID NO: 19;

[0176] the sequence of CDR1L comprises the sequence of SEQ ID NO: 41;

[0177] the sequence of CDR2L comprises the sequence of SEQ ID NO: 49; and

[0178] the sequence of CDR3L comprises the sequence of SEQ ID NO: 50.

[0179] In embodiments, the anti-PD-1 antibody, or antigen-binding fragment thereof, comprises:

[0180] a heavy chain variable region comprising SEQ ID NO: 20, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 20; and

[0181] a light chain variable region comprising SEQ ID NO: 51, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 51.

[0182] In embodiments, the CDRs of the anti-PD-1 antibody, or antigen-binding fragment thereof, comprise the following sequences:

[0183] the sequence of CDR1H, CDR2H and CDR3H comprise SEQ ID NOS: 17, 18, and 19, respectively; and

[0184] the sequence of CDR1L, CDR2L and CDR3L comprise respectively, SEQ ID NOS: 41, 42, and 43; SEQ ID NOS: 41, 52, and 53; SEQ ID NOS: 41, 55, and 56; or SEQ ID NOS: 58, 59, and 60.

[0185] In embodiments, the anti-PD-1 antibody, or antigen-binding fragment thereof, comprises:

[0186] a heavy chain variable region comprising SEQ ID NO: 20, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 20; and

[0187] a light chain variable region comprising SEQ ID NO: 44, 54, 57, or 61, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NO: 44, 54, 57, or 61.

[0188] In one aspect, the disclosure relates to a fusion protein comprising:

[0189] (i) an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprise a CDR1, CDR2, and CDR3; and wherein:

[0190] the sequence of CDR1H comprises the sequence of SEQ ID NO: 21;

[0191] the sequence of CDR2H comprises the sequence of SEQ ID NO: 22;

[0192] the sequence of CDR3H comprises the sequence of SEQ ID NO: 23;

[0193] the sequence of CDR1L comprises the sequence of SEQ ID NO: 96;

[0194] the sequence of CDR2L comprises the sequence of SEQ ID NO: 97; and

[0195] the sequence of CDR3L comprises the sequence of SEQ ID NO: 82;

[0196] (ii) an IL-15 polypeptide comprising the amino acid sequence of SEQ ID NO: 212, or an amino acid sequence that is at least 90% or at least 95% identical to SEQ ID NO: 212;

[0197] (iii) an IL-15Rα sushi domain polypeptide comprising the amino acid sequence of SEQ ID NO: 214, or an amino acid sequence that is at least 95% identical to SEQ ID NO: 214;

[0198] (iv) a first linker polypeptide joining the IL-15Rα sushi domain polypeptide and the IL-15 polypeptide; and

[0199] optionally wherein the anti-PD-1 antibody, or an antigen-binding fragment thereof, comprises two heavy chains, wherein:

[0200] (a) the CH3 domain of first heavy chain comprises the amino acid substitutions S354C and T366W (Kabat EU index numbering); and

[0201] (b) the CH3 domain of second heavy chain comprises the amino acid substitutions Y349C, T366S, L368A, and Y407V (Kabat EU index numbering).

[0202] In one aspect, the disclosure relates to a fusion protein comprising:

[0203] (i) an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprise a CDR1, CDR2, and CDR3; and wherein:

[0204] the sequence of CDR1H comprises the sequence of SEQ ID NO: 21;

[0205] the sequence of CDR2H comprises the sequence of SEQ ID NO: 22;

[0206] the sequence of CDR3H comprises the sequence of SEQ ID NO: 23;

[0207] the sequence of CDR1L comprises the sequence of SEQ ID NO: 96;

[0208] the sequence of CDR2L comprises the sequence of SEQ ID NO: 97; and

[0209] the sequence of CDR3L comprises the sequence of SEQ ID NO: 82;

[0210] (ii) an IL-15 polypeptide comprising the amino acid sequence of SEQ ID NO: 212, or an amino acid sequence that is at least 90% or at least 95% identical to SEQ ID NO: 212;

[0211] (iii) an IL-15Rα sushi domain polypeptide comprising the amino acid sequence of SEQ ID NO: 214, or an amino acid sequence that is at least 95% identical to SEQ ID NO: 214;

[0212] (iv) a first linker polypeptide joining the IL-15Rα sushi domain polypeptide and the IL-15 polypeptide; and

[0213] optionally wherein the anti-PD-1 antibody, or an antigen-binding fragment thereof, comprises two heavy chains, wherein:

[0214] (a) the CH3 domain of first heavy chain comprises the amino acid substitutions T350V, L351Y, F405A, and Y407V (Kabat EU index numbering); and

[0215] (b) the CH3 domain of second heavy chain comprises the amino acid substitutions T350V, T366L, K392L, and T394W (Kabat EU index numbering).

[0216] In one aspect, the disclosure relates to a fusion protein comprising:

[0217] (i) an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprise a CDR1, CDR2, and CDR3; and wherein:

[0218] the sequence of CDR1H comprises the sequence of SEQ ID NO: 21;

[0219] the sequence of CDR2H comprises the sequence of SEQ ID NO: 22;

[0220] the sequence of CDR3H comprises the sequence of SEQ ID NO: 23;

[0221] the sequence of CDR1L comprises the sequence of SEQ ID NO: 96;

[0222] the sequence of CDR2L comprises the sequence of SEQ ID NO: 97; and

[0223] the sequence of CDR3L comprises the sequence of SEQ ID NO: 82;

[0224] (ii) an IL-15 polypeptide comprising the amino acid sequence of SEQ ID NO: 212, or an amino acid sequence that is at least 90% or at least 95% identical to SEQ ID NO: 212;

[0225] (iii) an IL-15Rα sushi domain polypeptide comprising the amino acid sequence of SEQ ID NO: 214, or an amino acid sequence that is at least 95% identical to SEQ ID NO: 214;

[0226] (iv) a first linker polypeptide joining the IL-15Rα sushi domain polypeptide and the IL-15 polypeptide; and

[0227] optionally wherein the anti-PD-1 antibody, or an antigen-binding fragment thereof, comprises two heavy chains, wherein:

[0228] (a) the CH3 domain of first heavy chain comprises the amino acid substitutions L351Y, F405A, and Y407V (Kabat EU index numbering); and

[0229] (b) the CH3 domain of second heavy chain comprises the amino acid substitutions T366L, K392L, and T394W (Kabat EU index numbering).

[0230] In one aspect, the disclosure relates to a fusion protein comprising:

[0231] (i) an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprise a CDR1, CDR2, and CDR3; and wherein:

[0232] the sequence of CDR1H comprises the sequence of SEQ ID NO: 21;

[0233] the sequence of CDR2H comprises the sequence of SEQ ID NO: 22;

[0234] the sequence of CDR3H comprises the sequence of SEQ ID NO: 23;

[0235] the sequence of CDR1L comprises the sequence of SEQ ID NO: 96;

[0236] the sequence of CDR2L comprises the sequence of SEQ ID NO: 97; and

[0237] the sequence of CDR3L comprises the sequence of SEQ ID NO: 82;

[0238] (ii) an IL-15 polypeptide comprising the amino acid sequence of SEQ ID NO: 212, optionally wherein amino acid N65 of SEQ ID NO: 212 is substituted with an S, D, or A;

[0239] (iii) an IL-15Rα sushi domain polypeptide comprising the amino acid sequence of SEQ ID NO: 214, optionally wherein amino acid N28 of SEQ ID NO: 214 is substituted with an A;

[0240] (iv) a first linker polypeptide joining the IL-15Rα sushi domain polypeptide and the IL-15 polypeptide; and

[0241] optionally wherein the anti-PD-1 antibody, or an antigen-binding fragment thereof, comprises two heavy chains, wherein:

[0242] (a) the CH3 domain of first heavy chain comprises the amino acid substitutions S354C and T366W (Kabat EU index numbering); and

[0243] (b) the CH3 domain of second heavy chain comprises the amino acid substitutions Y349C, T366S, L368A, and Y407V (Kabat EU index numbering).

[0244] In one aspect, the disclosure relates to a fusion protein comprising:

[0245] (i) an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprise a CDR1, CDR2, and CDR3; and wherein:

[0246] the sequence of CDR1H comprises the sequence of SEQ ID NO: 21;

[0247] the sequence of CDR2H comprises the sequence of SEQ ID NO: 22;

[0248] the sequence of CDR3H comprises the sequence of SEQ ID NO: 23;

[0249] the sequence of CDR1L comprises the sequence of SEQ ID NO: 96;

[0250] the sequence of CDR2L comprises the sequence of SEQ ID NO: 97; and

[0251] the sequence of CDR3L comprises the sequence of SEQ ID NO: 82;

[0252] (ii) an IL-15 polypeptide comprising the amino acid sequence of SEQ ID NO: 212, optionally wherein amino acid N65 of SEQ ID NO: 212 is substituted with an S, D, or A;

[0253] (iii) an IL-15Rα sushi domain polypeptide comprising the amino acid sequence of SEQ ID NO: 214, optionally wherein amino acid N28 of SEQ ID NO: 214 is substituted with an A;

[0254] (iv) a first linker polypeptide joining the IL-15Rα sushi domain polypeptide and the IL-15 polypeptide; and

[0255] optionally wherein the anti-PD-1 antibody, or an antigen-binding fragment thereof, comprises two heavy chains, wherein:

[0256] (a) the CH3 domain of first heavy chain comprises the amino acid substitutions T350V, L351Y, F405A, and Y407V (Kabat EU index numbering); and

[0257] (b) the CH3 domain of second heavy chain comprises the amino acid substitutions T350V, T366L, K392L, and T394W (Kabat EU index numbering).

[0258] In one aspect, the disclosure relates to a fusion protein comprising:

[0259] (i) an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprise a CDR1, CDR2, and CDR3; and wherein:

[0260] the sequence of CDR1H comprises the sequence of SEQ ID NO: 21;

[0261] the sequence of CDR2H comprises the sequence of SEQ ID NO: 22;

[0262] the sequence of CDR3H comprises the sequence of SEQ ID NO: 23;

[0263] the sequence of CDR1L comprises the sequence of SEQ ID NO: 96;

[0264] the sequence of CDR2L comprises the sequence of SEQ ID NO: 97; and

[0265] the sequence of CDR3L comprises the sequence of SEQ ID NO: 82;

[0266] (ii) an IL-15 polypeptide comprising the amino acid sequence of SEQ ID NO: 212, optionally wherein amino acid N65 of SEQ ID NO: 212 is substituted with an S, D, or A;

[0267] (iii) an IL-15Rα sushi domain polypeptide comprising the amino acid sequence of SEQ ID NO: 214, optionally wherein amino acid N28 of SEQ ID NO: 214 is substituted with an A;

[0268] (iv) a first linker polypeptide joining the IL-15Rα sushi domain polypeptide and the IL-15 polypeptide; and

[0269] optionally wherein the anti-PD-1 antibody, or an antigen-binding fragment thereof, comprises two heavy chains, wherein:

[0270] (a) the CH3 domain of first heavy chain comprises the amino acid substitutions L351Y, F405A, and Y407V (Kabat EU index numbering); and

[0271] (b) the CH3 domain of second heavy chain comprises the amino acid substitutions T366L, K392L, and T394W (Kabat EU index numbering).

[0272] In one aspect, the disclosure relates to a fusion protein comprising:

[0273] (i) an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprise a CDR1, CDR2, and CDR3; and wherein:

[0274] the sequence of CDR1H comprise the sequence of SEQ ID NO: 17;

[0275] the sequence of CDR2H comprises the sequence of SEQ ID NO: 18;

[0276] the sequence of CDR3H comprises the sequence of SEQ ID NO: 19;

[0277] the sequence of CDR1L comprises the sequence of SEQ ID NO: 41;

[0278] the sequence of CDR2L comprises the sequence of SEQ ID NO: 49; and

[0279] the sequence of CDR3L comprises the sequence of SEQ ID NO: 50;

[0280] (ii) an IL-15 polypeptide comprising the amino acid sequence of SEQ ID NO: 212, or an amino acid sequence that is at least 90% or at least 95% identical to SEQ ID NO: 212;

[0281] (iii) an IL-15Rα sushi domain polypeptide comprising the amino acid sequence of SEQ ID NO: 214, or an amino acid sequence that is at least 95% identical to SEQ ID NO: 214;

[0282] (iv) a first linker polypeptide joining the IL-15Rα sushi domain polypeptide and the IL-15 polypeptide; and

[0283] optionally wherein the anti-PD-1 antibody, or an antigen-binding fragment thereof, comprises two heavy chains, wherein:

[0284] (a) the CH3 domain of first heavy chain comprises the amino acid substitutions S354C and T366W (Kabat EU index numbering); and

[0285] (b) the CH3 domain of second heavy chain comprises the amino acid substitutions Y349C, T366S, L368A, and Y407V (Kabat EU index numbering).

[0286] In one aspect, the disclosure relates to a fusion protein comprising:

[0287] (i) an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprise a CDR1, CDR2, and CDR3; and wherein:

[0288] the sequence of CDR1H comprise the sequence of SEQ ID NO: 17;

[0289] the sequence of CDR2H comprises the sequence of SEQ ID NO: 18;

[0290] the sequence of CDR3H comprises the sequence of SEQ ID NO: 19;

[0291] the sequence of CDR1L comprises the sequence of SEQ ID NO: 41;

[0292] the sequence of CDR2L comprises the sequence of SEQ ID NO: 49; and

[0293] the sequence of CDR3L comprises the sequence of SEQ ID NO: 50;

[0294] (ii) an IL-15 polypeptide comprising the amino acid sequence of SEQ ID NO: 212, or an amino acid sequence that is at least 90% or at least 95% identical to SEQ ID NO: 212;

[0295] (iii) an IL-15Rα sushi domain polypeptide comprising the amino acid sequence of SEQ ID NO: 214, or an amino acid sequence that is at least 95% identical to SEQ ID NO: 214;

[0296] (iv) a first linker polypeptide joining the IL-15Rα sushi domain polypeptide and the IL-15 polypeptide; and

[0297] optionally wherein the anti-PD-1 antibody, or an antigen-binding fragment thereof, comprises two heavy chains, wherein:

[0298] (a) the CH3 domain of first heavy chain comprises the amino acid substitutions T350V, L351Y, F405A, and Y407V (Kabat EU index numbering); and

[0299] (b) the CH3 domain of second heavy chain comprises the amino acid substitutions T350V, T366L, K392L, and T394W (Kabat EU index numbering).

[0300] In one aspect, the disclosure relates to a fusion protein comprising:

[0301] (i) an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprise a CDR1, CDR2, and CDR3; and wherein:

[0302] the sequence of CDR1H comprise the sequence of SEQ ID NO: 17;

[0303] the sequence of CDR2H comprises the sequence of SEQ ID NO: 18;

[0304] the sequence of CDR3H comprises the sequence of SEQ ID NO: 19;

[0305] the sequence of CDR1L comprises the sequence of SEQ ID NO: 41;

[0306] the sequence of CDR2L comprises the sequence of SEQ ID NO: 49; and

[0307] the sequence of CDR3L comprises the sequence of SEQ ID NO: 50;

[0308] (ii) an IL-15 polypeptide comprising the amino acid sequence of SEQ ID NO: 212, or an amino acid sequence that is at least 90% or at least 95% identical to SEQ ID NO: 212;

[0309] (iii) an IL-15Rα sushi domain polypeptide comprising the amino acid sequence of SEQ ID NO: 214, or an amino acid sequence that is at least 95% identical to SEQ ID NO: 214;

[0310] (iv) a first linker polypeptide joining the IL-15Rα sushi domain polypeptide and the IL-15 polypeptide; and

[0311] optionally wherein the anti-PD-1 antibody, or an antigen-binding fragment thereof, comprises two heavy chains, wherein:

[0312] (a) the CH3 domain of first heavy chain comprises the amino acid substitutions L351Y, F405A, and Y407V (Kabat EU index numbering); and

[0313] (b) the CH3 domain of second heavy chain comprises the amino acid substitutions T366L, K392L, and T394W (Kabat EU index numbering).

[0314] In one aspect, the disclosure relates to a fusion protein comprising:

[0315] (i) an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprise a CDR1, CDR2, and CDR3; and wherein:

[0316] the sequence of CDR1H comprise the sequence of SEQ ID NO: 17;

[0317] the sequence of CDR2H comprises the sequence of SEQ ID NO: 18;

[0318] the sequence of CDR3H comprises the sequence of SEQ ID NO: 19;

[0319] the sequence of CDR1L comprises the sequence of SEQ ID NO: 41;

[0320] the sequence of CDR2L comprises the sequence of SEQ ID NO: 49; and

[0321] the sequence of CDR3L comprises the sequence of SEQ ID NO: 50;

[0322] (ii) an IL-15 polypeptide comprising the amino acid sequence of SEQ ID NO: 212, optionally wherein amino acid N65 of SEQ ID NO: 212 is substituted with an S, D, or A;

[0323] (iii) an IL-15Rα sushi domain polypeptide comprising the amino acid sequence of SEQ ID NO: 214, optionally wherein amino acid N28 of SEQ ID NO: 214 is substituted with an A;

[0324] (iv) a first linker polypeptide joining the IL-15Rα sushi domain polypeptide and the IL-15 polypeptide; and

[0325] optionally wherein the anti-PD-1 antibody, or an antigen-binding fragment thereof, comprises two heavy chains, wherein:

[0326] (a) the CH3 domain of first heavy chain comprises the amino acid substitutions S354C and T366W (Kabat EU index numbering); and

[0327] (b) the CH3 domain of second heavy chain comprises the amino acid substitutions Y349C, T366S, L368A, and Y407V (Kabat EU index numbering).

[0328] In one aspect, the disclosure relates to a fusion protein comprising:

[0329] (i) an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprise a CDR1, CDR2, and CDR3; and wherein:

[0330] the sequence of CDR1H comprise the sequence of SEQ ID NO: 17;

[0331] the sequence of CDR2H comprises the sequence of SEQ ID NO: 18;

[0332] the sequence of CDR3H comprises the sequence of SEQ ID NO: 19;

[0333] the sequence of CDR1L comprises the sequence of SEQ ID NO: 41;

[0334] the sequence of CDR2L comprises the sequence of SEQ ID NO: 49; and

[0335] the sequence of CDR3L comprises the sequence of SEQ ID NO: 50;

[0336] (ii) an IL-15 polypeptide comprising the amino acid sequence of SEQ ID NO: 212, optionally wherein amino acid N65 of SEQ ID NO: 212 is substituted with an S, D, or A;

[0337] (iii) an IL-15Rα sushi domain polypeptide comprising the amino acid sequence of SEQ ID NO: 214, optionally wherein amino acid N28 of SEQ ID NO: 214 is substituted with an A;

[0338] (iv) a first linker polypeptide joining the IL-15Rα sushi domain polypeptide and the IL-15 polypeptide; and

[0339] optionally wherein the anti-PD-1 antibody, or an antigen-binding fragment thereof, comprises two heavy chains, wherein:

[0340] (a) the CH3 domain of first heavy chain comprises the amino acid substitutions T350V, L351Y, F405A, and Y407V (Kabat EU index numbering); and

[0341] (b) the CH3 domain of second heavy chain comprises the amino acid substitutions T350V, T366L, K392L, and T394W (Kabat EU index numbering).

[0342] In one aspect, the disclosure relates to a fusion protein comprising:

[0343] (i) an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprise a CDR1, CDR2, and CDR3; and wherein:

[0344] the sequence of CDR1H comprise the sequence of SEQ ID NO: 17;

[0345] the sequence of CDR2H comprises the sequence of SEQ ID NO: 18;

[0346] the sequence of CDR3H comprises the sequence of SEQ ID NO: 19;

[0347] the sequence of CDR1L comprises the sequence of SEQ ID NO: 41;

[0348] the sequence of CDR2L comprises the sequence of SEQ ID NO: 49; and

[0349] the sequence of CDR3L comprises the sequence of SEQ ID NO: 50;

[0350] (ii) an IL-15 polypeptide comprising the amino acid sequence of SEQ ID NO: 212, optionally wherein amino acid N65 of SEQ ID NO: 212 is substituted with an S, D, or A;

[0351] (iii) an IL-15Rα sushi domain polypeptide comprising the amino acid sequence of SEQ ID NO: 214, optionally wherein amino acid N28 of SEQ ID NO: 214 is substituted with an A;

[0352] (iv) a first linker polypeptide joining the IL-15Rα sushi domain polypeptide and the IL-15 polypeptide; and

[0353] optionally wherein the anti-PD-1 antibody, or an antigen-binding fragment thereof, comprises two heavy chains, wherein:

[0354] (a) the CH3 domain of first heavy chain comprises the amino acid substitutions L351Y, F405A, and Y407V (Kabat EU index numbering); and

[0355] (b) the CH3 domain of second heavy chain comprises the amino acid substitutions T366L, K392L, and T394W (Kabat EU index numbering).

[0356] In one embodiment, the anti-PD-1 antibody or antigen-binding fragment thereof provided by the disclosure is a multispecific or a bispecific antibody or antigen-binding fragment thereof. In one embodiment, the antibody or antigen-binding fragment is a bispecific antibody comprising a complementary region that binds to PD-L1 or PD-L2. The disclosure also provides conjugates of the antibodies or the fusion molecules, for example, and without limitation, to fluorescent labels, imaging agents, therapeutic agents, or cytotoxic agents.

[0357] The disclosure further provides pharmaceutical compositions comprising one or more of an anti-PD-1 antibody or antigen-binding fragment thereof, or fusion protein comprising an anti-PD-1 antibody or antigen-binding fragment thereof, and a pharmaceutically acceptable carrier.

[0358] In embodiments, the disclosure provides nucleic acid molecules encoding the anti-PD-1 antibodies or antigen-binding fragments thereof disclosed herein and nucleic acid molecules encoding the fusion proteins disclosed herein, as well as vectors comprising such nucleic acid molecules. Also provided are cells comprising a vector encoding the anti-PD-1 antibodies or antigen-binding fragments thereof disclosed herein, or the fusion proteins disclosed herein.

[0359] In embodiments, the disclosure provides a method of inhibiting binding of PD-1 to a ligand of PD-1, the method comprising administering to a subject in need thereof an effective amount of an anti-PD-1 antibody, or antigen-binding fragment thereof, or a fusion protein disclosed herein.

[0360] In embodiments, the disclosure provides a method of treating a disease in a subject in need thereof, the method comprising administering to said subject a therapeutically effective amount of a composition comprising an anti-PD-1 antibody, or antigen-binding fragment thereof, or a fusion protein disclosed herein in a pharmaceutically acceptable form.

[0361] In embodiments, the disclosure provides a method for increasing T cell activation in a subject in need thereof, the method comprising administering an effective amount of an anti-PD-1 antibody, or antigen-binding fragment thereof, or a fusion protein disclosed herein. In one embodiment, the disclosure provides a method of stimulating the immune system in a subject in need thereof, the method comprising administering to said subject an effective amount of a composition comprising an anti-PD-1 antibody, or antigen-binding fragment thereof, or a fusion protein disclosed herein in a pharmaceutically acceptable form. In one embodiment, the disclosure provides a method of reducing replication of a virus in a subject in need thereof, the method comprising administering to the subject an effective amount of a composition comprising an anti-PD-1 antibody, or antigen-binding fragment thereof, or a fusion protein disclosed herein.

[0362] The disclosure also provides a method of inhibiting the interaction of PD-1 with PD-L1 and/or PD-L2 in a subject, the method comprising administering to a subject in need thereof an effective amount of an anti-PD-1 antibody, or antigen-binding fragment thereof, or a fusion protein disclosed herein. The disclosure further provides a method of inhibiting immunosuppression mediated by PD-1 in a subject in need thereof, the method comprising administering to the subject an effective amount of an anti-PD-1 antibody, or antigen-binding fragment thereof, or a fusion protein disclosed herein.

[0363] The disclosure further provides a method of stimulating an immune response against a cell or tissue that expresses PD-1 in a subject in need thereof, the method comprising administering to the subject an effective amount of an anti-PD-1 antibody, or antigen-binding fragment thereof, or a fusion protein disclosed herein. In certain embodiments, the cell or tissue expressing PD-1 is a cancerous cell or a cell infected with a pathogen, including, but not limited to, a virus or a bacterium.

[0364] In one aspect, the present disclosure provides a method of treating cancer, an immune disorder, or an infection in a patient in need thereof, the method comprising (a) treating a cell, in vitro, with an anti-PD-1 antibody, or antigen-binding fragment thereof, or a fusion protein disclosed herein; and (b) administering the treated cell to the patient. In some embodiments, the cell is a T cell.

[0365] In another aspect, the disclosure provides a method of increasing T cell activation in response to an antigen in a subject, the method comprising administering to the subject an effective amount of an anti-PD-1 antibody, or antigen-binding fragment thereof, or a fusion protein disclosed herein, or a pharmaceutical composition disclosed herein.

[0366] In another aspect, the disclosure provides a method of treating a condition in a subject that would benefit from an upregulation of the subject's immune response, the method comprising administering to the subject an effective amount of an anti-PD-1 antibody, or antigen-binding fragment thereof, or a fusion protein disclosed herein. In certain embodiments, the subject has upregulated expression of PD-L1, or the subject has been identified as positive for expression of PD-L1.

[0367] In one embodiment, the disclosure provides methods of using the anti-PD-1 antibodies, or antigen-binding fragments thereof, or fusion proteins disclosed herein for treating a subject that does not respond to therapy with a checkpoint inhibitor (primary resistance), and/or for treating a subject that initially responds to checkpoint inhibitor treatment, but later becomes resistant to checkpoint inhibitor blockade (secondary or acquired resistance). Such methods for treating comprise administering to said subject an anti-PD-1 antibody, or antigen-binding fragment thereof, or a fusion protein disclosed herein. In some embodiments, the subject has acquired resistance to therapy with one or more of a PD-1 inhibitor, a PD-L1 inhibitor, and a CTLA-4 inhibitor.

[0368] In one embodiment, the disclosure provides a method of administering an anti-PD-1 antibody, or antigen-binding fragment thereof, or a fusion protein disclosed herein to a subject in need thereof, the method further comprising administering an additional therapeutic agent or therapy to the subject, wherein the additional therapeutic agent or therapy is selected from the group consisting of a cancer vaccine, a checkpoint inhibitor, an antibody to a tumor-specific antigen, a Bacillus Calmette-Guerin (BCG) vaccine, a cytotoxin, an interleukin 6 receptor (IL-6R) inhibitor, an interleukin 4 receptor (IL-4R) inhibitor, an IL-10 inhibitor, IL-2, IL-7, IL-21, IL-15, an antibody-drug conjugate, an anti-inflammatory drug, and a dietary supplement. In embodiments, the disclosure provides a method of administering an anti-PD-1 antibody, or antigen-binding fragment thereof, or a fusion protein disclosed herein to a subject in need thereof, the method further comprising administering to the subject a checkpoint inhibitor selected from a CTLA-4, a PD-1, a PD-L1, and a PD-L2 inhibitor. In embodiments, the disclosure provides a method of administering an anti-PD-1 antibody, or antigen-binding fragment thereof, or a fusion protein disclosed herein to a subject in need thereof, the method further comprising administering to the subject one or more of an inhibitor of LAG3, TIGIT, LAP, Podoplanin, Protein C receptor, ICOS, GITR, CD226, and/or CD160. In embodiments, the disclosure provides a method of administering an anti-PD-1 antibody, or antigen-binding fragment thereof, or a fusion protein disclosed herein to a subject in need thereof, the method further comprising administering an additional therapeutic agent or therapy, wherein the additional therapeutic agent or therapy is administered concurrently or consecutively with the anti-PD-1 antibody, or antigen-binding fragment thereof, or fusion protein disclosed herein. In embodiments, the disclosure provides a method of administering an anti-PD-1 antibody, or antigen-binding fragment thereof, or a fusion protein disclosed herein to a subject in need thereof, the method further comprising administering to the subject an additional therapeutic agent or therapy, wherein the additional therapeutic agent or therapy is administered separately, or as a mixture with the anti-PD-1 antibody, or antigen-binding fragment thereof, or fusion protein disclosed herein. In one embodiment, the disclosure provides a method of administering an anti-PD-1 antibody, or antigen-binding fragment thereof, or a fusion protein disclosed herein in combination with chemotherapy, radiotherapy, or surgery.

BRIEF DESCRIPTION OF THE FIGURES

[0369] FIG. **1**A, FIG. **1**B, FIG. **1**C, and FIG. **1**D show the heavy and light chain variable domain sequences and CDR sequences of anti-PD-1 antibodies disclosed herein. CDR sequences are according to Kabat (CDR sequences according to AbM/Chothia exclude the underlined amino acids). FIG. **1**A provides the heavy and light chain variable regions of six anti-human PD-1 (hPD-1) antibodies that were identified by library screening. FIG. **1**B provides the light chain and CDR sequences of 23H9 as well as of 23H9 variants that were identified by light chain shuffling, wherein a library of light chains was paired with the 23H9 heavy chain sequence. X_1 is Q or E; X_2 is H or Y; X_3 is Y or N; X_4 is T or N; X_5 is L, Q or E; X_6 is S, A, or V; X_7 is H, N, T, or S; X_8 is R or L; X_9 is G, A, or H; X_{10} is S or T; X_{11} is A, T, or S; and X_{12} is H or R. FIG. **1**C provides the light chain and CDR sequences of 24H9 as well as of 24H9 variants that were identified by light chain shuffling, wherein a library of light chains was paired with the 24H9 heavy chain sequence. X_{13} is A or V; X_{14} is S or G; X_{15} is Q, E, or R; X_{16} is G, S, D or N; X_{17} is G, S, or N; X_{18} is S, I, R, T, K, P, N, H, or V; X_{19} is L or V; X_{20} is G or A; X_{21} is S, D, E, or A; X_{22} is S or K; X_{23} is S, N, T, R, or D; X_{24} is L or V; X_{25} is Q, E, or H; X_{26} is S, N, A, R, P, or T; X_{27} is A or G; X_{28} is N, D, or Y; X_{29} is F or L; and X_{30} is A or T. FIG. **1**D provides sequences for hPD-1/mPD-1 cross-reacting antibody R3A9 as well as R3A9 derivatives that were identified by light chain shuffling, wherein a library of light chains was paired with the R3A9 heavy chain sequence.

[0370] FIG. **2**A and FIG. **2**B illustrate the binding of antibodies 19B6, 19B10, 23A8, 23H9, 24H9, and 23A11 to hPD-1-Fc (FIG. **2**A, labels as in FIG. **2**B) as determined by ELISA, and to hPD-1-his (FIG. **2**B).

[0371] FIG. **3** depicts the ability of antibodies 19B6, 19B10, 23A8, 23H9, 24H9, and 23A11 to block interaction between hPD-1 to hPD-L1.

[0372] FIG. **4**A, FIG. **4**B, and FIG. **4**C illustrate the binding of antibodies 19B6, 19B10, 23A8, 23H9, 24H9, and 23A11 to hPD-1-293 cells (FIG. **4**A), to SEB-activated PBMC from donor "EA" (low PD-1 expression) (FIG. **4**B), and to SEB-activated PBMC from donor "AF" (high PD-1 expression) (FIG. **4**C), respectively. FIG. **4**A: EC_{50} 23A8>23H9>19B10. MFI 23A8>23H9>19B10. FIG. **4**B: 23H9>24H9 and 23A8. FIG. **4**C: 23H9>24H9 and 23A8.

[0373] FIG. **5**A and FIG. **5**B illustrate the ability of antibodies 23A8 and 23H9 (FIG. **5**A) as well as 19B6 and 24H9 (FIG. **5**B) to block interactions between hPD-1 and hPD-L1.

[0374] FIG. **6**A, FIG. **6**B, FIG. **6**C, and FIG. **6**D depict binding of antibodies 23H9, 31B1, 33C4, 33G8, and 34C1 to hPD-1-Fc (FIG. **6**A, same labels as FIG. **6**B), binding to strepavidin-captured biotin-hPD-1-his (FIG. **6**B), binding to ahis-captured hPD-1-his (FIG. **6**C, same labels as FIG. **6**D), and blocking of hPD-1-Fc/hPD-L1-Fc interaction (FIG. **6**D). No significant difference was observed between the parental antibody 23H9 and its derivatives (FIG. **6**A and FIG. **6**B). All derivatives had lower EC_{50} and higher inhibition values than the parental antibody (FIG. **6**C and FIG. **6**D).

[0375] FIG. **7** depicts binding of antibodies 24H9, 32A11, 32D2, 32D11, 38A6, 38A10, 38A11, 38B2, 38C11, 39B3, 39B11, 39G8 and 38H11 to hPD-1-Fc (first, far left column), binding to strepavidin-captured hPD-1-his (second column), binding to ahis captured hPD-1-his (third column), and blocking of hPD-1/hPD-L1 interactions (fourth column).

[0376] FIG. **8**A, FIG. **8**B, FIG. **8**C, and FIG. **8**D depict binding of antibodies 31B1, 33C4, 23H9, 38A6, 24H9, and 38B2 to hPD-1-293 cells (FIG. **8**A, same labels as FIG. **8**B) and hPD-1 Jurkat cells (FIG. **8**B) as well as binding to SEB-activated PBMC from donor FA (FIG. **8**C, same labels as FIG. **8**D) and donor FB (FIG. **8**D). FIG. **8**A. MFI to hPD1-HEK293: 24H9 derivatives (38B2 and 38A6>24H9) >23H9 derivative (31B1 and 33C4>23H9). FIG. **8**B. MFI to hP01-Jurkat: 23H9 derivatives (33C4>31B1>23H9)>24H9 derivatives (38B2>38A6>24H9). FIG. **8**C and FIG. **8**D. EC_{50} value for binding to SEB-activated human PBMCs from two donors: 23H9 derivatives (31B1 same as 33C4) <24H9 derivatives (38A6 same as 31B1). MFI for binding to SEB-activated human PBMCs: 23H9 derivatives (31B1 same as 33C4)>24H9 derivatives (38A6 same as 31B1).

[0377] FIG. **9**A and FIG. **9**B illustrate the ability of antibodies 23H9, 31B1, 33C4, 24H9, 38B2, and 38A6 to block PD-1/PD-L1 interactions using a Promega binding assay. FIG. **9**A. EC_{50} of 23H9 and its derivatives 31B1 and 33C4: 31B1 (0.139 μg/ml)>33C4 (0.165 μg/ml)>23H9 (0.511 μg/ml). Maximum fold induction (luminescence): 31B1 (6.48)>33C4 (6.24)>23H9 (5.56). FIG. **9**B. EC_{50} of 24H9 and its derivatives 38A6 and 38B2: 38B2 (0.855 μg/ml)>38A6 (0.164 μg/ml)>24H9 (0.855 μg/ml). Maximum fold induction (luminescence): 38B2 (6.54)>38A6 (5.66)>24H9 (4.97).

[0378] FIG. **10**A, FIG. **10**B, and FIG. **10**C depict IL-2 accumulation for PBMCs from donor FA (FIG. **10**A) and IL-2 accumulation for PBMCs from donor EA (FIG. **10**B and FIG. **10**C), in presence of antibodies 23H9, 31B1, 24H9, and 38B2. FIG. **10**A. IL-2 accumulation in PBMCs from donor FA: IL-2 concentration increased in the presence of the indicated antibodies in a dose-dependent manner. FIG. **10**B. 23H9 and 31B1: EC_{50} was 0.344 and 0.107 nM, respectively; IL-2 concentration at 10 nM antibody concentration was 3.9 and 5.81 μg/ml, respectively. FIG. **10**C. 24H9 and 38B2: EC_{50} was >10 nM and 0.019 nM, respectively; IL-2 concentration at in 10 nM antibody concentration was 4.5 and 5.0 μg/ml, respectively.

[0379] FIG. **11** illustrates the thermo-stability measurement for antibodies 780_38 (31B1), 780_39 (33C4), 780_46 (38A6), and 780_54 (38B2) as determined by differential scanning calorimeter (DSC).

[0380] FIG. **12**A, FIG. **12**B, FIG. **12**C, FIG. **12**D, and FIG. **12**E depict binding of antibodies 31B1, 33C4, 38B2, and 38A6 to hPD-1FC (FIG. **12**A), streptavidin-captured biotin-labeled hPD-1his (FIG. **12**B, labels as in FIG. **12**A), and anti-his antibody captured hPD-1his (FIG. **12**C, labels as in FIG. **12**A) as well as blocking of hPD-1-hPD-L1 (FIG. **12**D) and hPD-1-hPD-L2 interactions (FIG. **12**E).

[0381] FIG. **13**A, FIG. **13**B, FIG. **13**C, and FIG. **13**D depict dose-response binding of antibodies 31B1, 33C4, 38A6, and 38B2 to hPD-1-293 cells (FIG. **13**A), hPD-1-Jurkat cells (FIG. **13**B), SEB-activated PBMCs from donor FA (FIG. **13**C), and SEB-activated PBMCs from donor FB (FIG. **13**D). FIG. **13**A. All antibody derivatives shown have similar EC_{50} values, but 24H9 derivatives 38A6 and 38B2 exhibit higher maximum binding signals. Same labels as in FIG. **13**B. FIG. **13**B. 23H9 derivatives 31B1 and 33C4 have lower EC_{50} values and higher maximum binding signals as compared to 24H9 derivatives 38A6 and 38B2. FIG. **13**C. Same labels as in FIG. **13**D. FIG. **13**C and FIG. **13**D. 23H9 derivatives 31B1 and 33C4 exhibit higher maximum binding signals and lower EC_{50} values as compared to 24H9 derivatives 38A6 and 38B2 as determined using PBMCs from two different donors.

[0382] FIG. **14**A and FIG. **14**B depict K_D values obtained for binding of antibodies 38B2, 38A6, 33C4, and 31B1 to hPD-1-his (FIG. **14**A) and hPD-1-Fc (FIG. **14**B) as determined by SPR.

[0383] FIG. **15**A and FIG. **15**B illustrate the ability of antibodies 31B1 and 38B2 to block intercellular hPD-1-hPD-L1 interactions. The EC_{50} values averaged from two experiments for 31B1 and 38B2 were 0.168 and 0.154 μg/ml, respectively. Fold induction of luminescence was also averaged from two experiments. No significant difference between 31B1 and 38B2 was observed. Both 31B1 and 38B2 were superior to control B (Nivolumab, sold under the brand name Opdivo) and similar to control M (Pembrolizumab, sold under the brand name Keytruda). FIG. **15**A. Experiment 1. FIG. **15**B. Experiment 2.

[0384] FIG. **16**A and FIG. **16**B illustrate the effect of anti-PD-1 antibodies 31Bland 38B2 on IL-2 cytokine production in SEB-activated PBMCs from donor EA (FIG. **16**A) and donor FA (FIG. **16**B). Cytokine IL-2 secretion was examined in SEB-activated human PBMC cells from donor EA and FA. The EC_{50} values for 38B2, 31B1, ctM and ctB were 0.101, 0.297, 0.210 and 0.548 nM (PBMC from donor EA). The maximum IL-2 secretion by cells treated by 38B2, 31B1, ctM or ctB was 8.05, 7.73, 7.21 and 6.79 ng/ml, respectively. 38B2 was more potent than 31B1 and two control antibodies; 31B1 was more potent than control B and comparable to control M.

[0385] FIG. **17**A, FIG. **17**B, FIG. **17**C, FIG. **17**D, FIG. **17**E, and FIG. **17**F depict the dose dependent binding of antibodies m3A7 and R3A9 to soluble mPD-1-Fc (FIG. **17**A), soluble strepatavidin-captured mPD-1-Fc (FIG. **17**B), soluble streptavidin-captured mPD-1-his (FIG. **17**C), cells expressing mPD-1 (FIG. **17**C) as well as blocking of mPD-1 to PD-L1 by antibodies m3A7 and R3A9 as determined by ELISA (FIG. **17**E) and blockage of intercellular mPD-1/PD-L1 interactions as determined by a Promega assay (FIG. **17**F).

[0386] FIG. **18**A, FIG. **18**B, FIG. **18**C, FIG. **18**D, and FIG. **18**E illustrate binding of antibodies 38B2, m2C1, m2A1, m4D1, m3A7, and R3A9 to hPD-1 (FIG. **18**A, labels as in FIG. **18**B), mPD-1 (FIG. **18**B), and streptavidin-captured biotin mPD-1 (FIG. **18**C, labels as in FIG. **18**B) as determined by ELISA as well as blocking of mPD-1-mPD-L1 interactions by antibodies 38B2, m2C1, m2A1, m4D1, m3A7, and R3A9 (FIG. **18**D, labels as in FIG. **18**E), and blocking of hPD-1-hPD-L1 interactions (FIG. **18**E) as determined by ELISA).

[0387] FIG. **19**A, FIG. **19**B, FIG. **19**C, and FIG. **19**D depict binding of antibodies m2A1, m2C1, m4D1, R3A9, m3A7 and 38B2 to cells expressing hPD-1 or mPD-1. Cells expressing human PD-1: hPD-293 (FIG. **19**A, labels as in FIG. **19**D) and hPD-1 Jurkat (FIG. **19**B, labels as in FIG. **19**D). Cells expressing murine PD-1: FIG. **19**C (labels as in FIG. **19**D) and FIG. **19**D.

[0388] FIG. **20**A and FIG. **20**B depict blocking of mPD-1/mPD-L1 interactions and blocking of hPD-1-hPD-L1 interactions by antibodies 38B2, m4D1, and m2C1. FIG. **20**A. Blockade: m4D1 was as potent as m3A7 in blocking mPDI-mPDL 1 interactions. IC50 m4D1=0.5724 nM. IC50 m3A7=0.5615 nM. IC50 m2C1=1.127 nM. FIG. **20**B. m4D1 blocks hPD1/hPDL 1 interactions but was not as potent as 38B2. IC50 38B2=0.7248 nM. IC50 m4D1=2.125 nM. IC50 m2C1=31.25 nM.

[0389] FIG. **21**A and FIG. **21**B depict schematic diagrams of exemplary PD-1/IL-15 fusion proteins.

[0390] FIG. **22**A, FIG. **22**B, FIG. **22**C, and FIG. **22**D depict binding of fusion proteins 1N-m3A7/IL-15, 2N-m3A7/IL-15, 1C-m3A7/IL-15, and 2C-m3A7/IL-15 to mPD-1 (FIG. **22**A) and to cells expressing mPD-1 (FIG. **22**B) as well as blocking of mPD-L1 to mPD-1 using a competition ELISA (FIG. **22**C) or a Promega blocking assay (FIG. **22**D).

[0391] FIG. **23**A, FIG. **23**B. and FIG. **23**C depict the effect of fusion proteins 1N-m3A7/IL-15, 2N-m3A7/IL-15, 1C-m3A7/IL-15, and 2C-3A7/IL-15 on proliferation of CTLL2 (FIG. **23**A) and C57BL6 (FIG. **23**B). FIG. **23**C. $CD8^+/CD4^+$ T cell populations in total spleen cells. Fusion

proteins 1N-DP47/IL-15, 2N-DP47/IL-15, 1C-DP47/IL-15, and 2C-DP47/IL-15 were used as controls.

[0392] FIG. **24** depicts the ability of anti-PD-L1/SD15 fusion proteins to reduce tumor growth of mice bearing PD-1 expressing tumors in a PD-1/PD-L1 resistant Lewis Lung Model (LL2).

[0393] FIG. **25**A and FIG. **25**B illustrate that, as compared to C-terminal fusions, N-terminal fusion proteins are particularly useful to act on tumor infiltrating lymphocytes (TILs) compared to peripheral T cells. This is due to the cis-presentation enabled by the N-terminal fusion constructs.

[0394] FIG. **26**A, FIG. **26**B, and FIG. **26**C illustrate blocking of PD-1/PD-L1 interactions (FIG. **26**A and FIG. **26**C) and PD-1/PD-L2 interactions (FIG. **26**B) for hPD-1fusion proteins (FIG. **26**A and FIG. **26**B) and mutated hPD-1 fusion proteins (comprising (38B2)/N65D/S/A-mutated IL-15) (FIG. **26**C).

[0395] FIG. **27**A, FIG. **27**B and FIG. **27**C illustrate stimulation of the proliferation of M07e cells by the indicated anti-PD-L1-SD15 fusion proteins.

[0396] FIG. **28** illustrates the impact of different of anti-PD-L1/IL-15/linker/IL-15Rα sushi domain fusion proteins on tumor size. A CT26 syngeneic model was used. Single dose, IV. Anti-PD-L1 antibody: D7A8.

[0397] FIG. **29**A, FIG. **29**B, FIG. **29**C, FIG. **29**D, FIGS. **29**E, and **29**F illustrate that the presence of an N65S mutation in IL-15 in a 1N-fusion protein does not affect the ability of the fusion to bind PD-1 and to disrupt PD-1 interactions. FIG. **29**A. Binding of 1N-fusion proteins to a soluble hPD-1-Fc. FIG. **29**B. ELISA competition assay for measuring PD-L1 binding to PD-1. FIG. **29**C. ELISA competition assay for measuring PD-L2 binding to PD-1.

[0398] FIG. **29**D. Binding of 1N-fusion proteins to hPD-1 transfected HEK293 cells. FIG. **29**E. Promega blockade assay to determine binding of PD-L2 to PD-1. FIG. **29**F. Promega blockade assay to determine binding of PD-L2 to PD-1. Fusion proteins comprising antibody DP47 (a non-targeting control antibody) served as controls. mut=N65S.

[0399] FIG. **30**A, FIG. **30**B, FIG. **30**C, FIG. **30**D, and FIG. **30**E illustrate that the presence of an N65S mutation in IL-15 in a 1N-fusion protein leads to significant potency decreases of the fusion protein in proliferating human cells. FIGS. **30**A, **30**B, and **30**C show stimulation of proliferation of M07e cells by anti-PD-1 (38B2)/N65D/S/A-mutated IL-15 fusions. Fusion proteins comprising a non-targeting control antibody served as controls (FIG. **30**B). FIG. **30**D shows proliferation of hPBMCs upon stimulation with the indicated fusion proteins. FIG. **30**E shows binding of the indicated fusion proteins to hIL2Rβ transfected HEK30 cells.

[0400] FIG. **31**A, FIG. **31**B, FIG. **31**C, and FIG. **31**D illustrate that the presence of an N65S mutation in IL-15 in a 1N-fusion protein leads to significant potency decreases of the fusion protein in proliferating murine cells and an increase in dose response in proliferating $CD8^+$ T cells than $CD4^+$ T cells. FIGS. **31**A and **31**B show proliferation of murine CTLL2 cells (FIG. **31**A) and murine BALB/c spleen cells (FIG. **31**B) upon stimulation with the indicated fusion proteins. FIGS. **31**C and **31**D show $CD8^+$ and $CD4^+$ T cell populations in murine BALB/c spleen cells (FIG. **31**C) and hPBMCs (FIG. **31**D) upon stimulation with the indicated fusion proteins.

[0401] FIG. **32**A, FIG. **32**B, FIG. **32**C, FIG. **32**D, FIG. **32**E, FIG. **32**F, FIG. **32**G, FIG. **32**H, FIG. **32**I, FIG. **32**J, and FIG. **32**K illustrate that 1N-fusion proteins comprising an IL-15 mutation exhibited strong anti-tumor activity in vivo in an anti-PD-1 antibody-resistant mouse model. FIGS. **32**A, FIG. **32**B, FIG. **32**F, FIG. **32**G, FIG. **32**I, and FIG. **32**K. Tumor volume after treatment with Keytruda or the indicated 1N-fusion proteins. mut=N65S mutation. ct=DP47=non-targeting control antibody. Ketruda=pembrolizumab (formerly lambrolizumab, brand name Keytruda). FIG. **32**C. Tumor growth for each mouse (N65S-38B2/IL-15, 12 mg/kg treatment). FIG. **32**D, FIG. **32**H, and FIG. **32**J. % change in body weight. FIG. **32**E. Mouse survival at different dose levels. FIGS. **32**A, FIG. **32**B, FIG. **32**C, FIG. **32**D, FIG. **32**E, FIG. **32**F, FIG. **32**G, FIG. **32**H, FIG. **32**I: Dosing was QW=once per week intraperitoneally for three weeks for 1N-fusion proteins, BIW=twice per week intraperitoneally for three weeks for controls. FIG. **32**J, and FIG. **32**K: Dosing was BIW=twice per week intraperitoneally for three weeks.

[0402] FIG. **33** shows that N65S-1N-38B2/IL-15 and N65D-1N-38B2/IL-15 fusion proteins prevent a re-challenge in mice bearing a hPDL1-CT26 tumor.

[0403] FIG. **34**A. FIG. **34**B, and FIG. **34**C show that 1N-fusion proteins comprising an IL-15 mutation exhibited improved anti-tumor activity in hPD1/PDL1 mice bearing hPDL1-CT26 tumor as compared to combinations of non-targeted fusion protein and an anti-PD-1 antibody. FIG. **34**A. Tumor volume after treatment with the indicated proteins. FIG. **34**B. Mouse survival after treatment with the indicated proteins. FIG. **34**C. % change in body weight after treatment with the indicated proteins.

[0404] FIG. **35**A. FIG. **35**B, and FIG. **35**C show that the additional administration of an anti-PD-1 antibody does not lead to a further increase in anti-tumor activity of 1N-fusion proteins. FIG. **35**A. Tumor volume after treatment with the indicated proteins. FIG. **35**B. Mouse survival after treatment with the indicated proteins. FIG. **35**C. % change in body weight after treatment with the indicated proteins.

[0405] FIG. **36**A and FIG. **36**B illustrate that N65S-1N-38B2/IL-15 exhibited a similar serum half-life profile as antibody 38B2 in both IV (FIG. **36**A) and IP (FIG. **36**B) injection with dose response up to 120 h after treatment.

[0406] FIG. **37**A, FIG. **37**B, FIG. **37**C, and FIG. **37**D illustrate the results of a mechanism of action study in hPDL1/PD1 transgenic BALB/c mice bearing hPDL1-CT26 tumors. FIG. **37**A. 0.5×10^6 of hPDL1/CT26 cells were subcutaneously inoculated to the right lower flank of the hPD1/PDL1 transgenic BALB/c mice. When the tumor size reached about 175 mms, the mice were intravenously injected with of (1) N65S-1N-38B2/IL-15 (0.06 μmol/kg and 0.035 μmol/kg, respectively), (2) N65S-1N-DP47/IL-15 (non-targeted control, 0.035 μmol/kg), (3) antibody 38B2 (0.035 μmol/kg) and (4) the combination of antibody 38B2 (0.035 μmol/kg) and N65S-1N-38B2/IL-15 (0.035 μmol/kg). FIG. **37**B. Blood and draining lymph node (DLN) from all groups were collected to perform flow cytometry. Tumors were collected to perform TILs analysis. FIG. **37**C. CD8/CD4 ratio in tumors, the blood, and draining lymph nodes (treated with antibody (1) 38B2, (2) PD1 targeted fusion protein N65S-1N-38B2/IL-15, (3) non-targeted fusion protein N65S-1N-DP47/IL-15, or (4) a combination of 38B2 and N65S-1N-38B2/IL-15). FIG. **37**D. Analysis of CD8 and CD4 subtypes in tumors (treated with antibody (1) 38B2, (2) PD1 targeted fusion protein N65S-1N-38B2/IL-15, (3) non-

targeted fusion protein N65S-1N-DP47/IL-15, or (4) a combination of 38B2 and N65S-1N-38B2/IL-15).

[0407] FIG. **38** illustrates that a N65S-1N-m3A7/IL-15 (surrogate) fusion protein showed significant anti-tumor efficacy in numerous mouse syngeneic tumor models. Data for EMT6 as shown as an illustrative example.

DETAILED DESCRIPTION

[0408] The present disclosure provides fusion proteins comprising an anti-PD-1 antibody or antigen-binding fragment thereof linked to an IL-15 polypeptide, which in turn is linked to an IL-15 receptor alpha (IL-15Rα) polypeptide comprising the IL-15Rα sushi domain. In addition, provided herein are antibodies, and antigen-binding fragments thereof, that specifically bind to PD-1 and fusion proteins comprising such anti-PD-1 antibodies and PD-1 binding fragments thereof.

[0409] Fusion Proteins Comprising Anti-PD-1 Antibodies or Antigen-Fragments Thereof

[0410] In one aspect, the disclosure provides fusion proteins comprising an antibody, or antigen-binding fragment thereof that binds to PD-1. This portion of the fusion protein can be any antibody or antibody fragment that specifically binds PD-1, including those comprising the corresponding heavy and light chain variable regions or CDRs provided in FIG. **1**, or otherwise described herein.

[0411] Disclosed herein are fusion proteins comprising a stimulatory domain. As used herein, a "stimulatory domain" is a domain that promotes an immune response. The stimulatory domain may stimulate an immune response mediated by, for example, inducing T cell or NK cell activity and/or proliferation. In embodiments, the stimulatory domain stimulates cells that respond to an interleukin or an interferon, such as, without limitation, IL-2, IL-7, IL-15, and IL-21. In one embodiment, the stimulatory domain binds to and stimulates a receptor that is responsive to an interleukin or an interferon, such as, without limitation, IL-2, IL-7, IL-13, IL-15, and IL-21. The stimulatory domain can also be a hybrid domain that is a hetero-complex of two or more ligands covalently linked to each other.

[0412] In embodiments, the stimulatory domain includes a sequence or domain that promotes IL-15 stimulation of the IL-15 receptor (IL-15R).

[0413] In one embodiment, the stimulatory domain that promotes IL-15R stimulation comprises IL-15 or an IL-15 derivative.

[0414] In one embodiment, the stimulatory domain that promotes IL-15R stimulation comprises an IL-15Rα polypeptide comprising the IL-15Rα sushi domain or a derivative thereof. In an embodiment, the stimulatory domain comprises the sushi domain of the IL-15Rα chain.

[0415] In an embodiment, the stimulatory domain comprises IL-15 or a derivative thereof, whose binding may be enhanced by the presence of an IL-15Rα polypeptide comprising the IL-15Rα sushi domain or a derivative thereof. In one embodiment, the stimulatory domain comprises a complex of IL-15 or a derivative thereof and an IL-15Rα polypeptide comprising the IL-15Rα sushi domain or a derivative thereof. In some embodiment, the stimulatory domain comprises an IL-15 or a derivative thereof and an IL-15Rα polypeptide comprising the IL-15Rα sushi domain or a derivative thereof, wherein the two polypeptides are covalently linked by a linker (including, but not limited to, a linker comprising SEQ ID NO: 215).

[0416] In one embodiment, the IL-15 or a derivative thereof is located N-terminally of the IL-15Rα polypeptide comprising the IL-15Rα sushi domain or derivative thereof. In one embodiment, the IL-15 or a derivative thereof is located C-terminally of the IL-15Rα polypeptide comprising the IL-15Rα sushi domain or derivative thereof. In one embodiment, the stimulatory domain comprises the sequence of the SD15 domain highlighted in any one of SEQ ID NOS:177-180.

[0417] As demonstrated herein, provided herein is a fusion protein which comprises (1) a PD-1 binding domain that blocks binding of PD-1 to PD-L1 and inhibits immunosuppression, and (2) a stimulatory domain that promotes an immune response, wherein the fusion proteins provides for increased immune cell activity, compared to two distinct molecules that provide the before mentioned functions separately. Specifically, the experiments disclosed herein demonstrate that fusion proteins containing both a PD-1 binding domain that blocks binding of PD-1 to PD-L1, and an stimulatory domain IL-15 or a derivative thereof and an IL-15Rα polypeptide comprising the IL-15Rα sushi domain or a derivative thereof, promoted increased proliferation, Th1 cytokine release, and killing activity-related molecules of NK and T cells, compared to providing the domains in separate molecules.

[0418] In certain embodiments, the fusion protein comprises a stimulatory domain disclosed herein that is covalently linked to an anti-PD-1 antibody or antigen-binding fragment thereof disclosed herein via a flexible linker. In some embodiments, provided herein is a fusion protein wherein the stimulatory domain disclosed herein is fused directly to an anti-PD-1 antibody or antigen-binding fragment disclosed herein.

[0419] As used herein, "covalently linked" or "fused" refers to the association of two or more polypeptides through a covalent bond. In some embodiments, two polypeptides that are covalently linked are fused to each other directly, i.e., without any additional polypeptide sequence between the first and the second peptide. Accordingly, in some embodiments, the N-terminus of the first polypeptide is fused directly to the C-terminus of the second polypeptide or vice versa. In other embodiments, the two polypeptides that are covalently linked are part of a continuous polypeptide chain, but are not directly fused to each other (i.e., the two polypeptides may be separated by one or more amino acids, a linker or another polypeptide). The term "covalently linked" does not imply a specific orientation of the two or more polypeptides that are fused to each other.

[0420] IL-15 is a 14-15 KD cytokine with structural similarity to IL-2. IL-15 is also known as MGC9721. A variety of cell types constitutively produce IL-15 mRNA, and these include monocytes, macrophages, DCs, keratinocytes, epidermal skin cells, fibroblasts, various epithelial cells, bone marrow stromal cells, and nerve cells. In addition, IL-15 mRNA is also produced in kidney, placenta, lung, heart, skeletal muscle, and brain tissues. However, only monocytes, DCs, epithelial cells, bone marrow stromal cells, fibroblasts, and very few other cells and tissues secrete detectable levels of IL-15. IL-15 and IL-2 are found to bind the same hematopoietin subunits and share many biological activities. IL-15 regulates T and NK cell activation and proliferation, and the number of $CD8^+$ memory cells is affected by a balance between IL-15 and IL-2. In embodiments, the IL-15 or IL-15 derivative disclosed herein has at

least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of the activity of human IL-15. IL-15 may be a mammalian IL-15, preferably a primate IL-15, and more preferably a human IL-15. The human IL-15 (Accession number NP_000576) amino acids sequence is provided as SEQ ID NO:212.

[0421] The term "IL-15 derivative" refers to a polypeptide having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity with SEQ ID NO:212, the mature form of human I1-15. Techniques for making such derivatives are known in the art. In some embodiments, the IL-15 or IL-15 derivative sequence may comprise one or more amino acid substitutions. In some embodiments, the amino acid substitutions are located at positions 1, 4, 8, 30, 45, 61, 64, 65, and/or 108 of IL-15 (residue numbers are referring to the mature form of the IL-15 protein). In some embodiments, the amino acid substitutions are located at position 45, 65, and/or 108 of IL-15. In some embodiments the amino acid substitutions in IL-15 are N1D, N4D, D8N, D30N, D61N, E64Q, L45A, N65S/A/D/K, and/or Q108S/E. In some embodiments, the amino acid substitutions in IL-15 are L45A, N65S/A/D/K, and/or Q108S. In embodiments, a fusion protein disclosed herein comprises an IL-15 polypeptide comprising one of the following amino acid substitutions: N65S, N65A, or N65D. In embodiments, a fusion protein disclosed herein comprises an IL-15 polypeptide comprising one or more of the following amino acid substitutions: L45A, N65S, N65A, or N65D, and Q108S.

[0422] The amino acid sequence of human IL-15Rα isoform 1 precursor (Accession number NP_002180) is provided in SEQ ID NO:213. The IL-15 receptor, i.e., IL-15 receptor complex, specifically binds IL-15 with high affinity and consists of a unique interleukin 15 receptor αsubunit, IL-2/IL-15Rβ, and the common 7-chain/IL-2RT subunit. IL-15Rα is expressed by mitogen-activated macrophages, NK cells, and $CD4^+$ and $CD8^+$ T cells. The human IL-15Rα consists of seven exons, and alternative mRNA splicing may result in eight molecular IL-15Rα isoforms with different extra or intracellular domains. Full-length isoforms consist of an extracellular portion containing a conserved protein binding motif (sushi domain), a trans-membrane domain, and an intracellular tail.

[0423] As used herein, the term "sushi domain" of IL-15Rα refers to a domain beginning at the first cysteine residue (C1) after the signal peptide of IL-15Rα and ending at the fourth cysteine residue (C4) after said signal peptide. The sushi domain corresponding to a portion of the extracellular region of IL-15Rα is involved in binding to IL-15. The sushi domain in the present disclosure has at at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of the activity of the sushi domain of the human IL-15Rα chain.

[0424] The amino acid sequence of human IL-15Rα isoform 1 precursor is provided in SEQ ID NO:213 (this sequence includes the signal sequence). The sushi domain amino acid sequence of human IL-15Rα is provided in SEQ ID NO: 214.

[0425] The term "IL-15Rα sushi domain derivative" or "IL-15Rα sushi domain variant" refers to a polypeptide having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity with the sequence of the human IL-15Rα sushi domain (SEQ ID NO:214). Techniques for making such derivatives or variants are known in the art. All such derivatives comprise the four cysteine residues of the sushi domain of IL-15Rα. In some such derivatives, naturally occurring amino acids may be replaced by chemically modified amino acids to alter the polypeptide half-life. In some embodiments, the IL-15Rα sushi domain or IL-15Rα sushi domain derivative sequence may comprise one or more amino acid substitutions. In some embodiments, the amino acid substitution is located at position 60 of IL-15Rα (numbering of the IL-15Rα residues include the signal peptide, see, e.g., SEQ ID NO:213). In some embodiments, the amino acid substitution in the IL-15Rα sushi domain is N60A (i.e., the asparagine (N) at amino acid 60 is substituted with alanine (A)).

[0426] IL-15 binds with high affinity to IL-15Rα, which then associates with an IL-15Rβ/γc complex expressed by the same target cell (cis-presentation). IL-15Rα is also known to trans-present IL-15 with high affinity to a different target cell expressing the IL-15Rβ/γ(c) complex (trans-presentation). IL-15 cis- and trans-presentation mechanisms lead to different dynamics of receptor activation and signal transduction, with cis-presentation inducing fast and transient responses, and trans-presentation inducing slower, more persistent ones.

[0427] In some embodiments, the fusion proteins disclosed herein comprise a stimulatory domain, which comprises a hybrid domain comprising the sushi domain of the IL-15Rα chain attached to IL-15 by a linker (including, but not limited to, the linker of SEQ ID NO: 215). In certain embodiments, the stimulatory domain disclosed herein is covalently linked to an anti-PD-1 antibody or antigen-binding fragment thereof disclosed herein via a second linker (including, but not limited to, the linker of SEQ ID NO: 216). In other embodiments, the stimulatory domain exemplified herein is directly fused to an anti PD-1 antibody or antigen-binding fragment disclosed herein.

[0428] In one embodiment, provided is an "N-terminal fusion protein," wherein a stimulatory domain is linked directly or via a linker (e.g., via one or more peptides) to the N-terminus of an anti-PD1 binding portion of the fusion protein (e.g., the N-terminus of a heavy chain of an anti-PD-1 antibody disclosed herein).

[0429] N-terminal fusion proteins include but are not limited to the following (exemplary) fusion proteins (components recited from N- to C-terminus, "-" indicated direct covalent linkage or linkage via a linker (e.g., via one or more peptides):

[0430] (1) (IL-15 or derivative thereof)—(heavy chain of anti-PD-1 antibody or antigen binding fragment thereof)

[0431] (2) (IL-15 or derivative thereof)—(light chain of anti-PD-1 antibody or antigen binding fragment thereof)

[0432] (3) (IL-15Rα polypeptide comprising the IL-15Rα sushi domain or a derivative thereof)—(IL-15 or derivative thereof)—(heavy chain of anti-PD-1 antibody or antigen binding fragment thereof)

[0433] (4) (IL-15Rα polypeptide comprising the IL-15Rα sushi domain or a derivative thereof)—(IL-15 or derivative thereof)—(light chain of anti-PD-1 antibody or antigen binding fragment thereof)

[0434] (5) (IL-15 or derivative thereof)—(IL-15Rα polypeptide comprising the IL-15Rα sushi domain or a derivative thereof)—(heavy chain of anti-PD-1 antibody or antigen binding fragment thereof)

[0435] (6) (IL-15 or derivative thereof)—(IL-15Rα polypeptide comprising the IL-15Rα sushi domain or a derivative thereof)—(light chain of anti-PD-1 antibody or antigen binding fragment thereof)

[0436] N-terminal fusion proteins may comprise more than one stimulatory domain.

[0437] In one embodiment, provided is a fusion protein, wherein the stimulatory domain is covalently linked to the N-terminus of one (and only one) of the heavy chains of the anti-PD-1 antibody or antigen binding fragment thereof. An N-terminal fusion protein comprising a single stimulatory domain is referred to as a "i-N-terminal fusion protein."

[0438] Provided herein is a fusion protein comprising (1) a stimulatory domain (2) a first heavy chain of an anti-PD-1 antibody or antigen binding fragment thereof, wherein the stimulatory domain is covalently linked to the N-terminus of the first heavy chain, and (3) a second heavy chain of an anti-PD-1 antibody or antigen binding fragment thereof, wherein the second heavy chain is not linked to a stimulatory domain. In some embodiments, the stimulatory domain comprises (i) IL-15 or a derivative thereof, or (ii) an IL-15Rα polypeptide comprising the IL-15Rα sushi domain or a derivative thereof, or (iii) both.

[0439] In one embodiment, provided is a fusion protein, wherein a stimulatory domain is covalently linked to the N-termini of both of the heavy chains of the anti-PD-1 antibody or antigen binding fragment thereof. An N-terminal fusion protein comprising two stimulatory domains, both linked to different antibody chains, is referred to as a "2-N-terminal fusion protein."

[0440] In one embodiment, provided is an "C-terminal fusion protein," wherein a stimulatory domain is linked directly or via a linker (e.g., via one or more peptides) to the C-terminus of an anti-PD1 binding portion of the fusion protein (e.g., the C-terminus of a heavy chain of an anti-PD-1 antibody disclosed herein).

[0441] C-terminal fusion proteins include but are not limited to the following (exemplary) fusion proteins (components recited from N- to C-terminus, "-" indicated direct covalent linkage or linkage via a linker (e.g., via one or more peptides):

[0442] (1) (heavy chain of anti-PD-1 antibody or antigen binding fragment thereof)—(IL-15 or derivative thereof)

[0443] (2) (light chain of anti-PD-1 antibody or antigen binding fragment thereof)—(IL-15 or derivative thereof)

[0444] (3) (heavy chain of anti-PD-1 antibody or antigen binding fragment thereof)—(IL-15Rα polypeptide comprising the IL-15Rα sushi domain or a derivative thereof)—(IL-15 or derivative thereof)

[0445] (4) (light chain of anti-PD-1 antibody or antigen binding fragment thereof)—(IL-15Rα polypeptide comprising the IL-15Rα sushi domain or a derivative thereof)—(IL-15 or derivative thereof)

[0446] (5) (heavy chain of anti-PD-1 antibody or antigen binding fragment thereof)—(IL-15 or derivative thereof)—(an IL-15Rα polypeptide comprising the IL-15Rα sushi domain or a derivative thereof)

[0447] (6) (light chain of anti-PD-1 antibody or antigen binding fragment thereof)—(IL-15 or derivative thereof)—(an IL-15Rα polypeptide comprising the IL-15Rα sushi domain or a derivative thereof)

[0448] C-terminal fusion proteins may comprise more than one stimulatory domain.

[0449] In one embodiment, provided is a fusion protein, wherein the stimulatory domain is covalently linked to the C-terminus one (and only one) of the heavy chains of the anti-PD-1 antibody or antigen binding fragment thereof. A C-terminal fusion protein comprising a single stimulatory domain is referred to as a "i-C-terminal fusion protein."

[0450] Provided herein is a fusion protein comprising (1) a stimulatory domain, (2) a first heavy chain of an anti-PD-1 antibody or antigen binding fragment thereof, wherein the stimulatory domain is covalently linked to the C-terminus of the first heavy chain, and (3) a second heavy chain of an anti-PD-1 antibody or antigen binding fragment thereof, wherein the second heavy chain is not linked to a stimulatory domain. In some embodiments, the stimulatory domain comprises (i) IL-15 or a derivative thereof, or (ii) an IL-15Rα polypeptide comprising the IL-15Rα sushi domain or a derivative thereof, or (iii) both.

[0451] In one embodiment, provided is a fusion protein, wherein a stimulatory domain is covalently linked to the C-termini of both of the heavy chains of the anti-PD-1 antibody or antigen binding fragment thereof. A C-terminal fusion protein comprising two stimulatory domains, both linked to different antibody chains, is referred to as a "2-C-terminal fusion protein."

[0452] FIG. **21** depicts schematic diagrams of exemplary fusion proteins as described herein.

[0453] Therapeutic levels of IL-2 are associated with high level of toxicity upon binding to the IL-2 receptor. Similarly, using therapeutic levels of IL-15 can also cause toxicity since IL-15 shares two receptor subunits with IL-2. The N-terminal fusion proteins, however, demonstrate reduced toxity compared to the C-terminal fusion proteins because when presented in cis position, the N-terminal IL-15 fusion proteins can selectively bind to tumor infiltrating lymphocyte (TIL) while showing a lower binding to peripheral T cells. When presented in cis position, N-terminal fusion proteins may bind to IL-15Rβγ and PD-1 simultaneously while reducing the IL-15Rβ/γ binding, allowing the N-terminal fusion proteins to selectively bind to TILs and promoting TIL proliferation. In contrast, C-terminal fusion proteins may bind to both peripheral T cells and TIL equally and may show higher toxicity than the N-terminal fusion proteins. (FIG. **25**). 1N-terminal fusion proteins show reduced toxicity compared to an N-terminal fusion protein comprising two stimulatory domains covalently linked to an anti-PD-1 antibody disclosed herein (2N-terminal fusion protein). Mutated N-terminal fusion proteins show a further reduction in toxicity due to even lower binding to peripheral T cells.

[0454] In one aspect, the disclosure relates to a fusion protein comprising:

[0455] (i) an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprise a CDR1, CDR2, and CDR3,

and wherein the antibody heavy chain comprises a constant region comprising three constant domains CH1, CH2, and CH3;

[0456] (ii) an interleukin 15 (IL-15) polypeptide comprising an amino acid sequence of SEQ ID NO: 212, or an amino acid sequence that is at least 90% or at least 95% identical to SEQ ID NO: 212;

[0457] (iii) an IL-15Rα sushi domain polypeptide comprising an amino acid sequence of SEQ ID NO: 214, or an amino acid sequence that is at least 90% or at least 95% identical to SEQ ID NO: 214; and

[0458] (iv) a first linker polypeptide joining the IL-15Rα sushi domain polypeptide and the IL-15 polypeptide.

[0459] The anti-PD-1 antibody, or antigen-binding fragment thereof, portion of the fusion protein can be any that specifically bind PD-1, including those comprising the corresponding variable regions or CDRs provided in FIG. **1**, or otherwise described herein. In embodiments, the fusion protein comprises an antibody, or antigen-binding fragment thereof, wherein the CDRs of the heavy and light chain variable regions comprise the following sequences: the sequence CDR1H comprises the sequence of SEQ ID NO: 21;

[0460] the sequence of CDR2H comprises the sequence of SEQ ID NO: 22;

[0461] the sequence of CDR3H comprises the sequence of SEQ ID NO: 23;

[0462] the sequence of CDR1L comprises the sequence $RX_{13}X_{14}X_{15}X_{16}IX_{17}X_{18}WX_{19}X_{20}$ (SEQ ID NO:135);

[0463] wherein X_{13} is A or V;

[0464] wherein X_{14} is S or G;

[0465] wherein X_{15} is Q, E, or R;

[0466] wherein X_{16} is G, S, D or N;

[0467] wherein X_{17} is G, S, or N;

[0468] wherein X_{18} is S, I, R, T, K, P, N, H, or V;

[0469] wherein X_{19} is L or V; and

[0470] wherein X_{20} is G or A; and

[0471] the sequence of CDR2L comprises the sequence $X_{21}AX_{22}X_{23}X_{24}X_{23}X_{26}$ (SEQ ID NO: 136); and

[0472] wherein X_{21} is S, D, E, or A;

[0473] wherein X_{22} is S or K;

[0474] wherein X_{23} is S, N, T, R, or D;

[0475] wherein X_{24} is L or V;

[0476] wherein X_{25} is Q, E, or H; and

[0477] wherein X_{26} is S, N, A, R, P, or T; and

[0478] the sequence of CDR3L comprises the sequence $QQX_{27}X_{28}SFPX_{29}X_{30}$ (SEQ ID NO: 137);

[0479] wherein X_{27} is A or G;

[0480] wherein X_{28} is N, D, or Y;

[0481] wherein X_{29} is F or L; and

[0482] wherein X_{30} is A or T.

[0483] In embodiments, the fusion protein comprises an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein the CDRs of the heavy and light chain variable regions comprise the following sequences:

[0484] the sequence of CDR1H comprises the sequence of SEQ ID NO: 21;

[0485] the sequence of CDR2H comprises the sequence of SEQ ID NO: 22;

[0486] the sequence of CDR3H comprises the sequence of SEQ ID NO: 23

[0487] the sequence of CDR1L comprises the sequence of SEQ ID NO: 96;

[0488] the sequence of CDR2L comprises the sequence of SEQ ID NO: 97; and

[0489] the sequence of CDR3L comprises the sequence of SEQ ID NO: 82.

[0490] In further embodiments, the fusion protein comprises an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein:

[0491] the heavy chain variable region comprises SEQ ID NO: 24, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 24; and

[0492] the light chain variable region comprises SEQ ID NO: 98, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 98.

[0493] In embodiments, the fusion protein comprises an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein the CDRs of the heavy chain and light chain variable regions comprise the following sequences:

[0494] the sequences of CDR1H, CDR2H and CDR3H comprise respectively SEQ ID NOS: 21, 22, and 23; and

[0495] the sequences of CDR1L, CDR2L and CDR3L comprise respectively, SEQ ID NOS: 45, 46, and 47; SEQ ID NOS: 66, 67, and 68; SEQ ID NOS: 70, 67, and 71; SEQ ID NOS: 73, 74, and 75; SEQ ID NOS: 77, 78, and 47; SEQ ID NOS: 80, 81, and 82; SEQ ID NOS: 77, 78, and 84; SEQ ID NOS: 77, 86, and 47; SEQ ID NOS: 88, 89, and 47; SEQ ID NOS: 66, 67, and 47; SEQ ID NOS: 80, 92, and 75; SEQ ID NOS: 80, 94, and 71; SEQ ID NOS: 99, 100, and 47; SEQ ID NOS: 102, 103, and 104; SEQ ID NOS: 106, 103, and 47; SEQ ID NOS: 108, 103, and 47; SEQ ID NOS: 110, 111, and 75; SEQ ID NOS: 77, 103, and 113; SEQ ID NOS: 77, 111, and 47; SEQ ID NOS: 116, 67, and 47; SEQ ID NOS: 118, 119, and 47; SEQ ID NOS: 80, 78, and 47; SEQ ID NOS: 122, 103 and 47; SEQ ID NOS: 124, 125, and 75; SEQ ID NOS: 127, 38, and 68; SEQ ID NOS: 129, 130, and 47; or SEQ ID NOS: 132, 133, and 75.

[0496] In further embodiments, the fusion protein comprises an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein:

[0497] the heavy chain variable region comprises SEQ ID NO: 24, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 24; and

[0498] the light chain variable region comprises SEQ ID NO: 48, 69, 72, 76, 79, 83, 85, 90, 91, 93, 101, 105, 107, 109, 112, 114, 115, 117, 120, 121, 123, 126, 128, 131, or 134, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NO: 48, 69, 72, 76, 79, 83, 85, 90, 91, 93, 101, 105, 107, 109, 112, 114, 115, 117, 120, 121, 123, 126, 128, 131, or 134.

[0499] In embodiments, the fusion protein comprises an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein the CDRs of the heavy and light chain variable regions comprise the following sequences:

[0500] the sequence of CDR1H comprises the sequence of SEQ ID NO: 17;

[0501] the sequence of CDR2H comprises the sequence of SEQ ID NO: 18;

[0502] the sequence of CDR3H comprises the sequence of SEQ ID NO: 19;

[0503] the sequence of CDR1L comprises the sequence $RSSX_1SLLX_2SNGX_3X_4YLD$ (SEQ ID NO:62),

[0504] wherein X_1 is Q or E;

[0505] wherein X_2 is H or Y;

[0506] wherein X_3 is Y or N; and

[0507] wherein X_4 is T or N;

[0508] the sequence of CDR2L comprises the sequence $X_5X_6SX_7X_8X_9X_{10}$ (SEQ ID NO: 63),

[0509] wherein X_5 is L, Q or E;

[0510] wherein X_6 is S, A, or V;

[0511] wherein X_7 is H, N, T, or S;

[0512] wherein X_8 is R or L;

[0513] wherein X_9 is G, A, or H; and

[0514] wherein X_{10} is S or T; and

[0515] the sequence of CDR3L comprises the sequence $MQGX_{11}X_{12}WPYT$ (SEQ ID NO: 64),

[0516] wherein X_{11} is A, T, or S; and

[0517] wherein X_{12} is H or R.

[0518] In embodiments, the fusion protein comprises an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein the CDRs of the heavy chain and light chain variable regions comprise the following sequences:

[0519] the sequence of CDR1H comprises the sequence of SEQ ID NO: 17;

[0520] the sequence of CDR2H comprises the sequence of SEQ ID NO: 18;

[0521] the sequence of CDR3H comprises the sequence of SEQ ID NO: 19;

[0522] the sequence of CDR1L comprises the sequence of SEQ ID NO: 41;

[0523] the sequence of CDR2L comprises the sequence of SEQ ID NO: 49; and

[0524] the sequence of CDR3L comprises the sequence of SEQ ID NO: 50.

[0525] In further embodiments, the fusion protein comprises an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein:

[0526] the heavy chain variable region comprises SEQ ID NO: 20, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 20; and

[0527] the light chain variable region comprises SEQ ID NO: 51, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 51.

[0528] In embodiments, the fusion protein comprises an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein the CDRs of the heavy chain and light chain variable regions comprise the following sequences:

[0529] the sequence of CDR1H, CDR2H and CDR3H comprise SEQ ID NOS: 17, 18, and 19, respectively; and

[0530] the sequence of CDR1L, CDR2L and CDR3L comprise respectively, SEQ ID NOS: 41, 42, and 43; SEQ ID NOS: 41, 52, and 53; SEQ ID NOS: 41, 55, and 56; or SEQ ID NOS: 58, 59, and 60.

[0531] In further embodiments the fusion protein comprises an anti-PD-1 antibody, or antigen-binding fragment thereof, wherein:

[0532] the heavy chain variable region comprises SEQ ID NO: 20, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 20; and

[0533] the light chain variable region comprises SEQ ID NO: 44, 54, 57, or 61, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NO: 44, 54, 57, or 61.

[0534] Provided herein is a fusion protein that comprises a sequence described in Tables 24-27.

[0535] Provided herein is a fusion protein that comprises a heavy chain comprising a sequence selected from the group consisting of SEQ ID NOS: 174-184, 187-190, 193-199, 206-211, 224-243. Provided herein is a fusion protein that comprises a light chain comprising a sequence selected from the group consisting of SEQ ID NOS: 170, 173, 186, 192, and 205.

[0536] Provided herein is a fusion protein that comprises a light chain and a heavy/heavy chain combination recited in Table 26.

[0537] Provided herein is a fusion protein that comprises a light chain and one or more heavy chains recited in Table 27.

[0538] In embodiments, provided is a fusion protein comprising a light chain sequence comprising SEQ ID NO:219 and/or SEQ ID NO:98 and:

[0539] (1) a first heavy chain sequence comprising SEQ ID NO:220 and a second heavy chain sequence comprising SEQ ID NO:224;

[0540] (2) a first heavy chain sequence comprising SEQ ID NO:221 and a second heavy chain sequence comprising SEQ ID NO:225;

[0541] (3) a first heavy chain sequence comprising SEQ ID NO:222 and a second heavy chain sequence comprising SEQ ID NO:226;

[0542] (4) a first heavy chain sequence comprising SEQ ID NO:223 and a second heavy chain sequence comprising SEQ ID NO:227.

[0543] In embodiments, provided is a fusion protein comprising a light chain sequence comprising SEQ ID NO:219 and/or SEQ ID NO:98 and:

[0544] (1) a first heavy chain sequence comprising SEQ ID NO:220 and a second heavy chain sequence comprising SEQ ID NO:228;

[0545] (2) a first heavy chain sequence comprising SEQ ID NO:221 and a second heavy chain sequence comprising SEQ ID NO:229;

[0546] (3) a first heavy chain sequence comprising SEQ ID NO:222 and a second heavy chain sequence comprising SEQ ID NO:230;

[0547] (4) a first heavy chain sequence comprising SEQ ID NO:223 and a second heavy chain sequence comprising SEQ ID NO:231;

[0548] (5) a first heavy chain sequence comprising SEQ ID NO:220 and a second heavy chain sequence comprising SEQ ID NO:236;

[0549] (6) a first heavy chain sequence comprising SEQ ID NO:221 and a second heavy chain sequence comprising SEQ ID NO:237;

[0550] (7) a first heavy chain sequence comprising SEQ ID NO:222 and a second heavy chain sequence comprising SEQ ID NO:238;

[0551] (8) a first heavy chain sequence comprising SEQ ID NO:223 and a second heavy chain sequence comprising SEQ ID NO:239;

[0552] (9) a first heavy chain sequence comprising SEQ ID NO:240 and a second heavy chain sequence comprising SEQ ID NO:241; or

[0553] (10) a first heavy chain sequence comprising SEQ ID NO:240 and a second heavy chain sequence comprising SEQ ID NO:242.

[0554] In embodiments, provided is a fusion protein comprising a light chain sequence comprising SEQ ID NO:219 and/or SEQ ID NO:98 and:

[0555] (1) a first heavy chain sequence comprising SEQ ID NO:220 and a second heavy chain sequence comprising SEQ ID NO:232;

[0556] (2) a first heavy chain sequence comprising SEQ ID NO:221 and a second heavy chain sequence comprising SEQ ID NO:233;

[0557] (3) a first heavy chain sequence comprising SEQ ID NO:222 and a second heavy chain sequence comprising SEQ ID NO:234;

[0558] (4) a first heavy chain sequence comprising SEQ ID NO:223 and a second heavy chain sequence comprising SEQ ID NO:235; or

[0559] (5) a first heavy chain sequence comprising SEQ ID NO:240 and a second heavy chain sequence comprising SEQ ID NO:243.

[0560] In embodiments, provided is a fusion protein comprising a light chain sequence comprising SEQ ID NO:219 and/or SEQ ID NO:98 and:

[0561] (1) a first heavy chain sequence comprising SEQ ID NO:220 and a second heavy chain sequence comprising SEQ ID NO:224; or a first heavy chain sequence comprising SEQ ID NO:221 and a second heavy chain sequence comprising SEQ ID NO:225; or

[0562] (2) a first heavy chain sequence comprising SEQ ID NO:222 and a second heavy chain sequence comprising SEQ ID NO:226; or a first heavy chain sequence comprising SEQ ID NO:223 and a second heavy chain sequence comprising SEQ ID NO:227.

[0563] In embodiments, provided is a fusion protein comprising a light chain sequence comprising SEQ ID NO:219 and/or SEQ ID NO:98 and:

[0564] (1) a first heavy chain sequence comprising SEQ ID NO:220 and a second heavy chain sequence comprising SEQ ID NO:228; or a first heavy chain sequence comprising SEQ ID NO:221 and a second heavy chain sequence comprising SEQ ID NO:229;

[0565] (2) a first heavy chain sequence comprising SEQ ID NO:222 and a second heavy chain sequence comprising SEQ ID NO:230; or a first heavy chain sequence comprising SEQ ID NO:223 and a second heavy chain sequence comprising SEQ ID NO:231;

[0566] (3) a first heavy chain sequence comprising SEQ ID NO:220 and a second heavy chain sequence comprising SEQ ID NO:236; or a first heavy chain sequence comprising SEQ ID NO:221 and a second heavy chain sequence comprising SEQ ID NO:237;

[0567] (4) a first heavy chain sequence comprising SEQ ID NO:222 and a second heavy chain sequence comprising SEQ ID NO:238; or a first heavy chain sequence comprising SEQ ID NO:223 and a second heavy chain sequence comprising SEQ ID NO:239;

[0568] (5) a first heavy chain sequence comprising SEQ ID NO:240 and a second heavy chain sequence comprising SEQ ID NO:241; or

[0569] (6) a first heavy chain sequence comprising SEQ ID NO:240 and a second heavy chain sequence comprising SEQ ID NO:242.

[0570] In embodiments, provided is a fusion protein comprising a light chain sequence comprising SEQ ID NO:219 and/or SEQ ID NO:98 and:

[0571] (1) a first heavy chain sequence comprising SEQ ID NO:220 and a second heavy chain sequence comprising SEQ ID NO:232; or a first heavy chain sequence comprising SEQ ID NO:221 and a second heavy chain sequence comprising SEQ ID NO:233;

[0572] (2) a first heavy chain sequence comprising SEQ ID NO:222 and a second heavy chain sequence comprising SEQ ID NO:234; or a first heavy chain sequence comprising SEQ ID NO:223 and a second heavy chain sequence comprising SEQ ID NO:235; or

[0573] (3) a first heavy chain sequence comprising SEQ ID NO:240 and a second heavy chain sequence comprising SEQ ID NO:243.

[0574] Antibodies and Antigen-Binding Fragments Thereof

[0575] The term antibody is used here in the broadest sense and includes monoclonal antibodies (including full length or intact monoclonal antibodies), polyclonal antibodies, bispecific antibodies, humanized antibodies, single chain antibodies, chimeric antibodies, synthetic antibodies, recombinant antibodies, hybrid antibodies, mutagenized antibodies and grafted antibodies (grafted antibodies), bispecific antibodies, a specific antibody portion (e.g., a domain antibody), as well as any antigen-binding portion thereof that competes with an intact antibody for specific binding, an antigen-binding portion thereof (e.g., paratopes, CDRs), and any other modified conformations of the immunoglobulin molecule comprising the antigen recognition site so long as they exhibit the desired biological activity and specificity. Accordingly, an antibody is an immunoglobulin molecule or fragment or derivative thereof including any polypeptide comprising an antigen-binding site, capable of specifically binding to a target through at least one antigen recognition site located in the variable region of the immunoglobulin molecule. The disclosed antibody can be murine, rat, human, or any other origin (including chimeric or humanized antibodies).

[0576] In certain embodiments, the framework regions of the antibody (or antigen-binding fragment thereof) may be identical to human germline sequences or may be naturally or artificially modified.

[0577] In one preferred embodiment, the disclosed antibody structures belong to the IgG class of immunoglobulin molecules. A standard IgG immunoglobulin molecule comprises two identical light chain polypeptides, and two identical heavy chain polypeptides. The molecular weight of the light chain polypeptide is around 23,000 Daltons and the molecular weight of the heavy chain polypeptide varies between 53,000-70,000 Daltons. The four chains are typically joined by disulfide bonds in a "Y" configuration.

[0578] Two heavy chains (HC) and two light chains (LC) of an immunoglobulin molecule are covalently bonded to each other, and the end portions of the two heavy chains are bonded to each other by covalent disulfide linkages or non-covalent linkages when the immunoglobulins are generated by either hybridomas, B cells, or genetically engineered host cells. The light and heavy chains both contain regions of structural and functional homology. The term

"variable" and "constant" are used functionally. Each heavy chain is comprised of a heavy chain variable region ("HCVR" or "VH") and a heavy chain constant region (comprised of domains CH1, CH2, and CH3). Each light chain is comprised of a light chain variable region ("LCVR or "VL") and a light chain constant region (CL). The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.

[0579] The variable region allows the antibody to recognize and specifically bind epitopes located on antigens. The variable domains of both the light (VL) and heavy (VH) chain portions determine antigen recognition and specificity. The antigen-binding site of an antibody is comprised of the VL domain and VH domain, or a subset of the CDRs. More specifically, the antigen-binding site is defined by one, two, or three CDRs on each of the VH and VL chains (i.e. CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3). Conversely, the constant domains of the light chain (CL) and the heavy chain (CH1, CH2, or CH3) confer biological properties such as secretion, transplacental mobility, Fc receptor binding, complement binding, and the like. By convention, the numbering of the constant region domains increases as they become more distal from the antigen-binding site or amino-terminus of the antibody.

[0580] As used herein, the term "Complementarity Determining Regions" (CDRs) refers to portions of an antibody variable domain that are (typically) involved in antigen binding. Each variable region has three non-consecutive CDRs, known as CDR1, CDR2, and CDR3. The CDRs are separated by structurally conserved regions called framework regions (FR-1, -2, -3, and -4) that form a "core" β-sheet structure displaying these loops on the surface of the variable domain. The six CDRs present in each antigen-binding domain are short, non-contiguous sequences of amino acids that are specifically positioned to form the antigen-binding domain as the antibody assumes its three dimensional configuration in an aqueous environment. The length and composition of the CDR sequences are highly variable, especially in the CDR3. The remainder of the amino acids located in the antigen-binding domains or the "framework" regions, show less inter-molecular variability. The antigen-binding domain formed by the positioned CDRs defines a surface complementary to the epitope on the immunoreactive antigen. This complementary surface promotes the non-covalent binding of the antibody to its cognate epitope. Each CDR can comprise amino acid residues from a CDR as defined by e.g. Kabat (i.e., about residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the light chain variable domain and 31-35 (H1), 50-65 (H2) and 95-102 (H3) in the heavy chain variable domain (Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1987, 1991)). Each CDR can also comprise amino acid residues from a "hypervariable loop" (i.e., about residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in the light chain variable domain and 26-32 (H1), 53-55 (H2) and 96-101 (H3) in the heavy chain variable domain (Chothia & Lesk 196 J. Mol. Biol. 901 (1987)). In some instances, a CDR can include amino acids from both a CDR region defined according to Kabat and a hypervariable loop. The Kabat numbering may not always correspond to the linear numbering on the amino acid residues due to a shortening of, or insertion into, a structural component, whether framework or CDR, of the basic variable domain structure. The correct Kabat numbering of residues may be determined for a given antibody or antigen-binding fragment thereof by alignment of residues of homology in the sequence of the antibody or antigen-binding fragment thereof with a "standard" Kabat numbered sequence or be defined according to ImMunoGeneTics (IMGT) system (Lefranc, M.-P. et al., Dev. Comp. Immunol., 27, 55-77 (2003)).

[0581] As used herein, the term "antigen-binding portion" or "antigen-binding fragment" may be a fragment comprising a Fab, Fab', F(ab')2, Fd, Fv, domain antibodies (dAbs such as shark and camel antibodies), ScFv, a maxibody, a minibody, a nanobody, an intrabody, a diabody, a triabody, a tetrabody, a v-NAR and a bis-scFv, or a polypeptide that contain at least certain portions of an immunoglobulin sufficient to confer specific antigen-binding to the polypeptide.

[0582] The antibody may be any class of antibody, such as IgG, IgA, or IgM (or a subclass thereof), and the antibody need not be of any particular class, and any of the immunoglobulin molecules comprising the antigen recognition site of the required specificity, other modified configurations (including glycosylation variants of antibodies, amino acid sequence variants of antibodies, and covalently modified antibodies) can be encompassed. Modified versions of each of these classes and isotypes are known to a person skilled in the art, accordingly, are within the scope of the instant disclosure.

[0583] In some embodiments of the aspects described herein, the anti-PD-1 antibody fragment is a Fab fragment, which comprises or consist essentially of a variable (VL) and constant (CL) domain of the light chain and a variable domain (VH) and the first constant domain (CH1) of the heavy chain.

[0584] In some embodiments of the aspects described herein, the anti-PD-1 antibody fragment is a Fab' fragment, which refers to a Fab fragment having one or more cysteine residues at the C-terminus of the CH1 domain.

[0585] In some embodiments of the aspects described herein, the anti-PD-1 antibody fragment is an Fd fragment comprising or consisting essentially of VH and CH1 domains.

[0586] In some embodiments of the aspects described herein, the anti-PD-1 antibody fragment is an Fd' fragment comprising VH and CH1 domains and one or more cysteine residues at the C-terminus of the CH1 domain.

[0587] Single-chain Fv or scFv antibody fragments comprise or consist essentially of the VH and VL domains of an antibody, such that these domains are present in a single polypeptide chain. Generally, an Fv polypeptide further comprises a polypeptide linker between the VH and VL domains, which allows the scFv to form the desired structure for antigen-binding. Accordingly, in some embodiments of the aspects described herein, the anti-PD-1 antibody fragment is a Fv fragment comprising or consisting essentially of the VL and VH domains of a single arm of an antibody.

[0588] In some embodiments of the aspects described herein, the anti-PD-1 antibody fragment is a diabody comprising two antigen-binding sites, comprising a heavy chain

variable domain (VH) connected to a light chain variable domain (VL) in the same polypeptide chain.

[0589] In some embodiments of the aspects described herein, the anti-PD-1 antibody fragment is a dAb fragment comprising or consisting essentially of a VH domain.

[0590] In some embodiments of the aspects described herein, the anti-PD-1 antibody fragment is a F(ab')2 fragment, which comprises a bivalent fragment comprising two Fab' fragments linked by a disulfide bridge at the hinge region.

[0591] In some embodiments of the aspects described herein, the anti-PD-1 antibody fragment is a linear antibody comprising a pair of tandem Fd segments (VH-CH1-VH-CH1) which, together with complementary light chain polypeptides, form a pair of antigen-binding regions.

[0592] A person skilled in the arts can use various techniques that have been developed and are available for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies. However, F(ab')2 fragments can be isolated directly from recombinant host cell culture. Other techniques for the production of antibody fragments will be apparent to the skilled practitioner. In other embodiments, the antibody fragment of choice is a single chain Fv fragment (scFv). See, for example, WO 93/16185. Alternatively, these fragments can also be produced directly by recombinant host cells. For example, antibody fragments can be isolated from the antibody phage libraries discussed herein. In another approach, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form F(ab')2 fragments (Carter et al., 1992).

[0593] In one embodiment, the antibody is a bispecific antibody comprising a complementary region that binds PD-1.

[0594] Contemplated antibodies or antigen-binding fragments may have all types of constant regions, including IgM, IgG, IgD, and IgE, and any isotype, including IgG1, IgG2, IgG3, and IgG4. In one embodiment, the isotype is human IgG1. In another embodiment, the human isotype IgG4 is used. Light chain constant regions can be X or u. The antibody or antigen-binding fragment thereof may comprise sequences from more than one class or isotype.

[0595] Anti-PD-1 Antibodies and PD-1 Binding Fragments Thereof

[0596] The disclosure describes antibodies that bind to PD-1, and antigen-binding fragments thereof that bind to PD-1, as well as fusion proteins comprising such anti-PD-1 antibodies or antigen-binding fragments thereof. The term "PD-1" refers to programmed death-1 protein (also known as CD279), a T cell co-inhibitor. The term PD-1 encompasses recombinant PD-1 and/or a fragment thereof. The term also includes PD-1 or a fragment thereof coupled to, for example, mouse or human Fc, histidine tag, and/or a signal sequence. The term may further encompass a fusion protein comprising PD-1. The amino acid sequence of full-length PD-1 is provided in GenBank as accession number NP_005009.2. The ligands for PD-1 include PD-L1 and PD-L2. The amino acid sequence of full-length PD-L1 is provided in GenBank as accession number NP_054862.1. The amino acid sequence of full-length PD-L2 is provided in GenBank as accession number NP_079515.2.

[0597] In embodiments, the anti-PD-1 antibody or antigen binding fragment thereof specifically binds to PD-1 and antagonizes PD-1 mediated immune suppression. The anti-PD-1 antibodies and antigen-binding fragments thereof disclosed herein may interrupt, inhibit, or reduce PD-1 biological activity including downstream events mediated by PD-1. The anti-PD-1 antibodies and antigen-binding fragments thereof disclosed herein may exhibit any one or more of the following features: (a) binding to PD-1 and blocking of downstream signaling events; (b) blocking PD-L1-binding to PD-1; (c) increasing T cell proliferation; (d) upregulating the T cell-mediated immune response; (e) stimulating TNF secretion; (f) reducing inhibitory signal transduction through PD-1; and/or (g) stimulating IFNγ secretion. The anti-PD-1 antibodies and antigen-binding fragments thereof disclosed herein exhibit potent binding and inhibitory activities and are useful for therapeutic and diagnostics uses.

[0598] In one aspect, the disclosure provides antibodies and antigen-binding fragments thereof that bind to PD-1. In certain embodiments, the disclosure provides bispecific antibodies and binding proteins that bind specifically to PD-1 and at least one other molecule.

[0599] In another aspect the disclosure provides an antibody, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof binds to PD-1, and wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region wherein each of the heavy chain and the light chain variable regions comprise a CDR1, CDR2, and CDR3 and wherein the antibody heavy chain comprises a constant region comprising three constant domains CH1, CH2, and CH3.

[0600] In embodiments, the CDRs of the anti-PD-1 antibody, or antigen-binding fragment thereof, comprise the following sequences:

[0601] the sequence of CDR1H comprises the sequence of SEQ ID NO: 21;

[0602] the sequence of CDR2H comprises the sequence of SEQ ID NO: 22;

[0603] the sequence of CDR3H comprises the sequence of SEQ ID NO: 23;

[0604] the sequence of CDR1L comprises the sequence $RX_{13}X_{14}X_{15}X_{16}IX_{17}X_{15}WX_{19}X_{20}$ (SEQ ID NO:135);

[0605] wherein X_{13} is A or V;

[0606] wherein X_{14} is S or G;

[0607] wherein X_{15} is Q, E, or R;

[0608] wherein X_{16} is G, S, D or N;

[0609] wherein X_{17} is G, S, or N;

[0610] wherein X_{18} is S, I, R, T, K, P, N, H, or V;

[0611] wherein X_{19} is L or V; and

[0612] wherein X_{20} is G or A; and

[0613] the sequence of CDR2L comprises the sequence $X_{21}AX_{22}X_{23}X_{24}X_{23}X_{26}$ (SEQ ID NO: 136); and

[0614] wherein X_{21} is S, D, E, or A;

[0615] wherein X_{22} is S or K;

[0616] wherein X_{23} is S, N, T, R, or D;

[0617] wherein X_{24} is L or V;

[0618] wherein X_{25} is Q, E, or H; and

[0619] wherein X_{26} is S, N, A, R, P, or T; and

[0620] the sequence of CDR3L comprises the sequence $QQX_{27}X_{28}SFPX_{29}X_{30}$ (SEQ ID NO: 137);

[0621] wherein X_{27} is A or G;

[0622] wherein X_{28} is N, D, or Y;

[0623] wherein X_{29} is F or L; and

[0624] wherein X_{30} is A or T.

[0625] In embodiments, the CDRs of the anti-PD-1 antibody, or antigen-binding fragment thereof, comprise the following sequences:

[0626] the sequence of CDR1H comprises the sequence of SEQ ID NO: 21;

[0627] the sequence of CDR2H comprises the sequence of SEQ ID NO: 22;

[0628] the sequence of CDR3H comprises the sequence of SEQ ID NO: 23

[0629] the sequence of CDR1L comprises the sequence of SEQ ID NO: 96;

[0630] the sequence of CDR2L comprises the sequence of SEQ ID NO: 97; and

[0631] the sequence of CDR3L comprises the sequence of SEQ ID NO: 82.

[0632] In embodiments, the antibody, or antigen-binding fragment thereof, comprises:

[0633] a heavy chain variable region comprising SEQ ID NO: 24, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 24; and

[0634] a light chain variable region comprising SEQ ID NO: 98, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 98.

[0635] In embodiments, the CDRs of the anti-PD-1 antibody, or antigen-binding fragment thereof, comprise the following sequences:

[0636] the sequences of CDR1H, CDR2H and CDR3H comprise respectively SEQ ID NOS: 21, 22, and 23; and

[0637] the sequences of CDR1L, CDR2L and CDR3L comprise respectively, SEQ ID NOS: 45, 46, and 47; SEQ ID NOS: 66, 67, and 68; SEQ ID NOS: 70, 67, and 71; SEQ ID NOS: 73, 74, and 75; SEQ ID NOS: 77, 78, and 47; SEQ ID NOS: 80, 81, and 82; SEQ ID NOS: 77, 78, and 84; SEQ ID NOS: 77, 86, and 47; SEQ ID NOS: 88, 89, and 47; SEQ ID NOS: 66, 67, and 47; SEQ ID NOS: 80, 92, and 75; SEQ ID NOS: 80, 94, and 71; SEQ ID NOS: 99, 100, and 47; SEQ ID NOS: 102, 103, and 104; SEQ ID NOS: 106, 103, and 47; SEQ ID NOS: 108, 103, and 47; SEQ ID NOS: 110, 111, and 75; SEQ ID NOS: 77, 103, and 113; SEQ ID NOS: 77, 111, and 47; SEQ ID NOS: 116, 67, and 47; SEQ ID NOS: 118, 119, and 47; SEQ ID NOS: 80, 78, and 47; SEQ ID NOS: 122, 103 and 47; SEQ ID NOS: 124, 125, and 75; SEQ ID NOS: 127, 38, and 68; SEQ ID NOS: 129, 130, and 47; or SEQ ID NOS: 132, 133, and 75.

[0638] In embodiments, the anti-PD-1 antibody, or antigen-binding fragment thereof, comprises:

[0639] a heavy chain variable region comprising SEQ ID NO: 24, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 24; and

[0640] a light chain variable region comprising SEQ ID NO: 48, 69, 72, 76, 79, 83, 85, 90, 91, 93, 101, 105, 107, 109, 112, 114, 115, 117, 120, 121, 123, 126, 128, 131, or 134, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NO: 48, 69, 72, 76, 79, 83, 85, 90, 91, 93, 101, 105, 107, 109, 112, 114, 115, 117, 120, 121, 123, 126, 128, 131, or 134.

[0641] In embodiments, the CDRs of the anti-PD-1 antibody, or antigen-binding fragment thereof, comprise the following sequences:

[0642] the sequence of CDR1H comprises the sequence of SEQ ID NO: 17;

[0643] the sequence of CDR2H comprises the sequence of SEQ ID NO: 18;

[0644] the sequence of CDR3H comprises the sequence of SEQ ID NO: 19;

[0645] the sequence of CDR1L comprises the sequence $RSSX_1SLLX_2SNGX_3X_4YLD$ (SEQ ID NO:62),

[0646] wherein X_1 is Q or E;

[0647] wherein X_2 is H or Y;

[0648] wherein X_3 is Y or N; and

[0649] wherein X_4 is T or N;

[0650] the sequence of CDR2L comprises the sequence $X_5X_6SX_7X_8X_9X_{10}$ (SEQ ID NO: 63),

[0651] wherein X_5 is L, Q or E;

[0652] wherein X_6 is S, A, or V;

[0653] wherein X_7 is H, N, T, or S;

[0654] wherein X_8 is R or L;

[0655] wherein X_9 is G, A, or H; and

[0656] wherein X_{10} is S or T; and

[0657] the sequence of CDR3L comprises the sequence $MQGX_{11}X_{12}WPYT$ (SEQ ID NO: 64),

[0658] wherein X_{11} is A, T, or S; and

[0659] wherein X_{12} is H or R.

[0660] In embodiments, the CDRs of the anti-PD-1 antibody, or antigen-binding fragment thereof, comprise the following sequences:

[0661] the sequence of CDR1H comprises the sequence of SEQ ID NO: 17;

[0662] the sequence of CDR2H comprises the sequence of SEQ ID NO: 18;

[0663] the sequence of CDR3H comprises the sequence of SEQ ID NO: 19;

[0664] the sequence of CDR1L comprises the sequence of SEQ ID NO: 41;

[0665] the sequence of CDR2L comprises the sequence of SEQ ID NO: 49; and

[0666] the sequence of CDR3L comprises the sequence of SEQ ID NO: 50.

[0667] In embodiments, the anti-PD-1 antibody, or antigen-binding fragment thereof, comprises:

[0668] a heavy chain variable region comprising SEQ ID NO: 20, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 20; and

[0669] a light chain variable region comprising SEQ ID NO: 51, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 51.

[0670] In embodiments, the CDRs of the anti-PD-1 antibody, or antigen-binding fragment thereof, comprise the following sequences:

[0671] the sequence of CDR1H, CDR2H and CDR3H comprise SEQ ID NOS: 17, 18, and 19, respectively; and

[0672] the sequence of CDR1L, CDR2L and CDR3L comprise respectively, SEQ ID NOS: 41, 42, and 43; SEQ ID NOS: 41, 52, and 53; SEQ ID NOS: 41, 55, and 56; or SEQ ID NOS: 58, 59, and 60.

[0673] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds

to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 8, 12, 16, 20, and 24, and wherein the sequence of the light chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a light chain variable region amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 32, 36, 40, 44, 48, 51, 54, 57, 61, 65, 69, 72, 76, 79, 83, 85, 88, 90, 91, 93, 95, 98, 101, 105, 107, 109, 112, 114, 115, 117, 120, 121, 123, 126, 128, 131, 134, and 138.

[0674] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 20, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 65.

[0675] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence SEQ ID NO: 20; and wherein the sequence of the light chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a light chain variable region amino acid sequence selected from the group consisting of SEQ ID NOs: 44, 51, 54, 57, and 61.

[0676] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 20, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 51.

[0677] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 20, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 54.

[0678] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 20, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 57.

[0679] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 20, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 61.

[0680] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 138.

[0681] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence SEQ ID NO: 20; and wherein the sequence of the light chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a light chain variable region amino acid sequence selected from the group consisting of SEQ ID NOs: 69, 72, 76, 79, 83, 85, 87, 90, 91, 93, 95, 98, 101, 105, 107, 109, 112, 114, 115, 117, 120, 121, 123, 126, 128, 131, 134, and 138.

[0682] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain

variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 98.

[0683] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 69.

[0684] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 72.

[0685] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 76.

[0686] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 79.

[0687] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 83.

[0688] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 85.

[0689] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 87.

[0690] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 90.

[0691] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 91.

[0692] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds

to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 93.

[0693] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 95.

[0694] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 101.

[0695] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 105.

[0696] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 107.

[0697] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 109.

[0698] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 112.

[0699] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 114.

[0700] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 115.

[0701] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at

least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 117.

[0702] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 120.

[0703] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 121.

[0704] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 123.

[0705] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 126.

[0706] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 128.

[0707] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 131.

[0708] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 24, and wherein the sequence of the light chain variable region comprises the sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the light chain variable region amino acid sequence of SEQ ID NO: 134.

[0709] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the sequence of the heavy chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the heavy chain variable region amino acid sequence of SEQ ID NO: 142, and wherein the sequence of the light chain variable region comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a light chain variable region amino acid sequence selected from the group consisting of SEQ ID NOs: 146, 150, 153, 156, 160, 164, and 167.

[0710] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprises a CDR1, CDR2, and CDR3, and wherein:

[0711] the sequence of CDR1H comprises the sequence, SEQ ID NO: 139;

[0712] the sequence of CDR2H comprises the sequence, SEQ ID NO: 140;

[0713] the sequence of CDR3H comprises the sequence, SEQ ID NO: 141;

[0714] the sequence of CDR1L comprises the sequence, SEQ ID NO: 143;

[0715] the sequence of CDR2L comprises the sequence, SEQ ID NO: 144; and

[0716] the sequence of CDR3L comprises the sequence, SEQ ID NO: 145.

[0717] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds

to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprises a CDR1, CDR2, and CDR3, and wherein:

[0718] the sequence of CDR1H comprises the sequence, SEQ ID NO: 139;

[0719] the sequence of CDR2H comprises the sequence, SEQ ID NO: 140;

[0720] the sequence of CDR3H comprises the sequence, SEQ ID NO: 141;

[0721] the sequence of CDR1L comprises the sequence, SEQ ID NO: 147;

[0722] the sequence of CDR2L comprises the sequence, SEQ ID NO: 148; and

[0723] the sequence of CDR3L comprises the sequence, SEQ ID NO: 149.

[0724] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprises a CDR1, CDR2, and CDR3, and wherein:

[0725] the sequence of CDR1H comprises the sequence, SEQ ID NO: 139;

[0726] the sequence of CDR2H comprises the sequence, SEQ ID NO: 140;

[0727] the sequence of CDR3H comprises the sequence, SEQ ID NO: 141;

[0728] the sequence of CDR1L comprises the sequence, SEQ ID NO: 151;

[0729] the sequence of CDR2L comprises the sequence, SEQ ID NO: 148; and

[0730] the sequence of CDR3L comprises the sequence, SEQ ID NO: 152.

[0731] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprises a CDR1, CDR2, and CDR3, and wherein:

[0732] the sequence of CDR1H comprises the sequence, SEQ ID NO: 139;

[0733] the sequence of CDR2H comprises the sequence, SEQ ID NO: 140;

[0734] the sequence of CDR3H comprises the sequence, SEQ ID NO: 141;

[0735] the sequence of CDR1L comprises the sequence, SEQ ID NO: 154;

[0736] the sequence of CDR2L comprises the sequence, SEQ ID NO: 148; and

[0737] the sequence of CDR3L comprises the sequence, SEQ ID NO: 155.

[0738] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprises a CDR1, CDR2, and CDR3, and wherein:

[0739] the sequence of CDR1H comprises the sequence, SEQ ID NO: 139;

[0740] the sequence of CDR2H comprises the sequence, SEQ ID NO: 140;

[0741] the sequence of CDR3H comprises the sequence, SEQ ID NO: 141;

[0742] the sequence of CDR1L comprises the sequence, SEQ ID NO: 157;

[0743] the sequence of CDR2L comprises the sequence, SEQ ID NO: 158; and

[0744] the sequence of CDR3L comprises the sequence, SEQ ID NO: 159.

[0745] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprises a CDR1, CDR2, and CDR3, and wherein:

[0746] the sequence of CDR1H comprises the sequence, SEQ ID NO: 139;

[0747] the sequence of CDR2H comprises the sequence, SEQ ID NO: 140;

[0748] the sequence of CDR3H comprises the sequence, SEQ ID NO: 141;

[0749] the sequence of CDR1L comprises the sequence, SEQ ID NO: 161;

[0750] the sequence of CDR2L comprises the sequence, SEQ ID NO: 162; and

[0751] the sequence of CDR3L comprises the sequence, SEQ ID NO: 163.

[0752] In one embodiment, the disclosure provides an antibody or antigen-binding fragment thereof, which binds to PD-1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein each of the heavy chain and the light chain variable regions comprises a CDR1, CDR2, and CDR3, and wherein:

[0753] the sequence of CDR1H comprises the sequence, SEQ ID NO: 139;

[0754] the sequence of CDR2H comprises the sequence, SEQ ID NO: 140;

[0755] the sequence of CDR3H comprises the sequence, SEQ ID NO: 141;

[0756] the sequence of CDR1L comprises the sequence, SEQ ID NO: 157;

[0757] the sequence of CDR2L comprises the sequence, SEQ ID NO: 165; and

[0758] the sequence of CDR3L comprises the sequence, SEQ ID NO: 166.

[0759] In addition to the above description, FIG. **1** shows the heavy and light chain variable regions and associated CDR of antibodies disclosed herein as does the accompanying sequence listing, which is incorporated by reference in its entirety. As shown in the Examples below, light chain shuffling of an anti-PD-1 antibody led to the identification of antibody variants that conferred substantial improvements in PD-1 binding affinity. Analysis of the variants revealed certain CDR positions at which amino acids remained relatively unchanged among the light chain shuffled antibodies and other CDR positions at which variation could be introduced without abolishing PD-1 binding.

[0760] The anti-PD-1 antibodies and antigen-binding fragments thereof disclosed herein and the fusion proteins disclosed herein can have one or more amino acid substitutions, deletions, insertions, and/or additions. In some

embodiments, one or more CDR residues of the anti-PD-1 antibodies or antigen-binding fragments (or the fusion proteins comprising the anti-PD-1 antibodies or antigen-binding fragments) disclosed herein have been changed by amino acid substitution, deletion, insertion, and/or addition. Amino acid substitutions can be conservative or non-conservative substitutions. The present disclosure also includes anti-PD-1 antibodies, and antigen-binding fragments thereof (and the fusion proteins comprising the anti-PD-1 antibodies or antigen-binding fragments), which are derived from the amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are mutated to the corresponding residue(s) of the germline sequence from which the antibody was derived, or to the corresponding residue(s) of another human germline sequence, or to a conservative amino acid substitution of the corresponding germline residue(s) (such sequence changes are referred to herein collectively as "germline mutations"). In certain embodiments, the anti-PD-1 antibodies or binding fragments thereof (or the fusion proteins comprising the anti-PD-1 antibodies or antigen-binding fragments) comprise one or more CDRs, or one or more variable domains with an amino acid sequence at least 85% at least 90%, at least 95%, at least 97%, at least 98%, or at least 99%, identical to the CDR and/or variable domain sequences set forth in FIG. **1**.

[0761] Also provided herein variable heavy chain and variable light chain sequences as well as pairing thereof that are similar, but not identical to the variable heavy chain and variable light chains disclosed in Table 25 and pairings thereof. It will be evident that any of the frameworks described herein can be utilized in combination with any of the CDRs and CDR motifs described herein. In some embodiments, the anti-PD-1 antibody or antigen-binding fragment thereof utilizes a framework described in Table 25.

[0762] Also provided herein is a chimeric antigen receptor (CAR) comprising one, two, three, four, five, or six CDRs of the anti-PD1 antibodies and antigen binding fragments disclosed herein. Also provided herein is CAR comprising the six CDRs of any one of the anti-PD1 antibodies and antigen binding fragments disclosed herein.

[0763] Disclosed is an immune cell expressing a CAR comprising one, two, three, four, five, or six CDRs of the anti-PD1 antibodies and antigen binding fragments disclosed herein. Disclosed is an immune cell expressing a CAR comprising the six CDRs of any one of the anti-PD1 antibodies and antigen binding fragments disclosed herein. In some embodiments, the immune cell is a T cell.

[0764] "Identity" refers to the number or percentage of identical positions shared by two amino acid or nucleic acid sequences in optimally aligned sequences after considering number of gaps and the length of each gap that were needed for the optimal alignment. "Substantially identical" means an amino acid sequence, which differs from the original sequence only by conservative amino acid substitutions, which do not destroy the function of the protein.

[0765] Also disclosed herein are anti-PD-1 antibodies or antigen-binding fragments thereof or fusion proteins comprising an amino acid sequence that is at least 80%, or at least 85%, or at least 90%, or at least 95%, or at least 98%, or at least 99% identical to an amino acid sequence disclosed herein. Methods and computer programs for determining sequence similarity are publically available, including, but not limited to, the GCG program package (Devereux et al., Nucleic Acids Research 12: 387, 1984), BLASTP, BLASTN, FASTA (Altschul et al., J. Mol. Biol. 215:403 (1990), and the ALIGN program (version 2.0). The Smith Waterman algorithm may also be used to determine similarity. The BLAST program is publicly available from NCBI and other sources (BLAST Manual, Altschul, et al., NCBI NLM NIH, Bethesda, Md. 20894; BLAST 2.0 at http://www.ncbi.nlm.nih.gov/blast/). In comparing sequences, these methods account for various substitutions, deletions, and other modifications.

[0766] In some embodiments of the aspects described herein, amino acid sequence modification(s) of the antibodies or antigen-binding fragments thereof that bind to PD-1 or the fusion proteins that bind to PD-1 described herein are contemplated. Amino acid sequence variants of the anti-PD-1 antibody or antigen-binding fragment thereof or the fusion proteins are prepared by introducing appropriate nucleotide changes into the nucleic acid encoding the anti-PD-1 antibody or antigen-binding fragment thereof or the fusion protein, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of, residues within the amino acid sequences of the antibody or antigen-binding fragment thereof. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, if the final construct possesses the desired characteristics, e.g., binding specificity, inhibition of biological activity.

[0767] Amino acid substitutions can be made, in some cases, by selecting substitutions that do not differ significantly in their effect on maintaining (a) the structure of the peptide backbone in the area of the substitution, (b) the charge or hydrophobicity of the molecule at the target sit; or (c) the bulk of the side chain (conservative amino acid substitution variant. These variants have at least one amino acid residue in the antibody or antigen-binding fragment thereof or fusion protein replaced by a different residue that has similar side chain properties. Amino acids can be grouped according to similarities in the properties of their side chains (see Lehninger, BIOCHEMISTRY (2nd ed., Worth Publishers, New York, 1975):

[0768] (1) non-polar: Ala (A), Val (V), Leu (L), Ile (I), Pro (P), Phe (F), Trp (W), Met (M);

[0769] (2) uncharged polar: Gly (G), Ser (S), Thr (T), Cys (C), Tyr (Y), Asn (N), Gln (Q);

[0770] (3) acidic: Asp (D), Glu (E);

[0771] (4) basic: Lys (K), Arg (R), His (H).

[0772] As such, a non-limiting example for a conservative amino acid substitution is one that replaces a non-polar amino acid with another non-polar amino acid.

[0773] Alternatively, naturally occurring residues can be divided into groups based on common side-chain properties:

[0774] (1) hydrophobic: Ala (A), Val (V), Leu (L), Ile (I), Met (M);

[0775] (2) neutral hydrophilic: Ser (S), Thr (T), Cys (C), Asn (N), Gln (Q);

[0776] (3) acidic: Asp (D), Glu (E);

[0777] (4) basic: Lys (K), Arg (R), His (H);

[0778] (5) residues that influence chain orientation: Gly (G), Pro (P);

[0779] (6) aromatic: Phe (F), Trp (W), Tyr (Y).

[0780] Substitutions made within these groups can be considered conservative substitutions. Examples of non-limiting substitutions include, substitution of valine for alanine, lysine for arginine, glutamine for asparagine, glu-

tamic acid for aspartic acid, serine for cysteine, asparagine for glutamine, aspartic acid for glutamic acid, proline for glycine, arginine for histidine, leucine for isoleucine, isoleucine for leucine, arginine for lysine, leucine for methionine, leucine for phenylalanine, glycine for proline, threonine for serine, serine for threonine, tyrosine for tryptophan, phenylalanine for tyrosine, and/or leucine for valine.

[0781] Further contemplated are amino acid sequence insertions, which can include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal fusions include an antibody or antigen-binding fragment thereof with an N-terminal methionyl residue or an antibody or antigen-binding fragment thereof fused to a cytotoxic polypeptide (or fusion proteins comprising such antibody or antigen-binding fragment thereof). Other examples of terminal fusions of the antibody or antigen-binding fragment thereof include the fusion to the N- or C-terminus of the antibody or antigen-binding fragment thereof to an enzyme or a polypeptide which increases the serum half-life of the antibody or antigen-binding fragment thereof, such as, for example, biotin (or fusion proteins comprising such antibody or antigen-binding fragment thereof).

[0782] Any cysteine residue not involved in maintaining the proper conformation of the antibodies or antigen-binding fragments thereof that bind to PD-1 also can be substituted, for example with a serine or an alanine, to improve the oxidative stability of the molecule and prevent aberrant crosslinking.

[0783] Conversely, cysteine bond(s) can be added to the anti-PD-1 antibody or antigen-binding fragment thereof to improve its stability (particularly where the anti-PD-1 antibody or antigen-binding fragment thereof is an antibody fragment such as an Fv fragment).

[0784] In some embodiments, the anti-PD-1 antibodies or antigen-binding fragments thereof or the fusion protein comprising antibodies or antigen-binding fragments thereof describes have amino acid alterations that alter the original glycosylation pattern of the anti-PD-1 antibody or antigen-binding fragment thereof. By "altering the original glycosylation pattern" is meant deleting one or more carbohydrate moieties found in the antibody or antigen-binding fragment thereof, and/or adding one or more glycosylation sites that are not present in the antibody or antigen-binding fragment thereof. Glycosylation of antibodies is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine-X-serine and asparagine-X-threonine, wherein X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-aceylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine can also be used. The alteration can also be made by the addition of, or substitution by, one or more serine or threonine residues to the sequence of the original antibody or antigen-binding fragment thereof (for O-linked glycosylation sites).

[0785] In some embodiments, the anti-PD-1 antibody or antigen-binding fragment thereof may include a modification, including, but not limited to glycosylation, acetylation, pegylation, phosphorylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. The process of chemical modifications are known in the art, which may include, but are not limited to, specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the molecules may contain one or more non-classical amino acids.

[0786] The anti-PD-1 antibodies and antigen-binding fragments thereof disclosed herein may include anti-PD-1 antibodies and antigen-binding fragments thereof whose binding characteristics have been altered by direct mutation, affinity maturation, phage display, or chain shuffling. The affinity and specificity may be altered by mutating CDRs and screening for CDRs with desired characteristics. Methods of mutagenesis are known to one of skill in the art.

[0787] Antibody Binding

[0788] Also provided herein are anti-PD-1 antibodies and antigen-binding fragments thereof, and fusion proteins comprising anti-PD-1 antibodies or antigen-binding fragments thereof, that bind to the same epitope on PD-1 as one of the anti-PD-1 antibodies or antigen-binding fragments thereof disclosed herein.

[0789] In some embodiments, the anti-PD-1 antibodies and antigen-binding fragments thereof provided herein bind selectively to PD-1 over one or more PD family members. In one embodiment, the anti-PD-1 antibody or antigen-binding fragment thereof does not exhibit significant binding to other PD family members, including to CTLA-4 and/or CD28. The human PD-1 gene produces four alternatively spliced PD-1 mRNA transcripts. One of these variants produces a soluble form of PD-1. In one aspect, the disclosure provides anti-PD-1 antibodies or antigen-binding fragments thereof that bind to all isoforms of PD-1. In some embodiments, the provided anti-PD-1 antibodies and antigen-binding fragments thereof bind to mammalian PD-1.

[0790] As used herein, "binding" of an antibody or antigen-binding fragment thereof, or fusion protein comprising an antibody or antigen-binding fragment thereof, to PD-1, an epitope on PD-1, or, in certain embodiments described below, particular residues on PD-1, includes the selective interaction of the antibody or antigen-binding fragment thereof with PD-1. Binding therefore includes, e.g., primary and secondary interactions including hydrogen bonds, ionic interactions, salt bridges, as well as hydrophilic and hydrophobic interactions.

[0791] In certain embodiments, the anti-PD-1 antibodies or antigen-binding fragments thereof described herein bind to PD-1 with an equilibrium constant for the dissociation (K_D) of 10^{-2} to 10^{-10} mol/l, 10^{-3} to 10^{-10} mol/l, 10^{-4} to 10^{-10} mol/l, 10^{-5} to 10^{-10} mol/l, 10^{-6} to 10^{-10} mol/l, 10^{-7} to 10^{-10} mol/l, 10^{-8} to 10^{-10} mol/l or 10^{-9} to 10^{-10} mol/l. In other embodiments, the anti-PD-1 antibodies or antigen-binding fragments thereof described herein bind to PD-1 with a K_D of 10^{-2} to 10^{-9} mol/l, 10^{-3} to 10^{-9} mol/l, 10^{-4} to 10^{-9} mol/l, 10^{-5} to 10^{-9} mol/l, 10^{-6} to 10^{-9} mol/l, 10^{-7} to 10^{-9} mol/l, 10^{-8} to 10^{-9} mol/l, or 10^{-9} 10^{-10} mol/l.

[0792] As used herein, "affinity," represented by the K_D of an antigen with an antigen-binding protein, is a measure of the binding strength between an antigenic determinant and an antigen-binding site on the antigen-binding protein, such

as an antibody or antibody fragment thereof. The value of K_D is inversely proportional to the binding strength between an antigenic determinant and the antigen-binding molecule. Alternatively, the affinity can also be expressed as the association constant (K_A), which is $1/K_D$). Affinity can be determined in a manner known per se, depending on the specific antigen of interest by a person skilled in the art.

[0793] The term "specificity" herein refers to the ability of an antibody or antigen-binding fragment thereof, such as an anti-PD-1 antibody or antigen-binding fragment thereof, to recognize an epitope within PD-1, while only having little or no detectable reactivity with other portions of PD-1. Specificity can be relatively determined by competition assays or by epitope identification/characterization techniques described herein or their equivalents known in the art.

[0794] The term "epitope" herein refers to the specific target to which an antibody binds. Epitopes can be formed both by a contiguous stretch of amino acids (continuous epitopes) and by three-dimensional arrangement of amino acid residues that exists only when the target protein is folded in a particular conformation (discontinuous epitopes.) In general, an epitope comprises at least 3 amino acids, at least 4, at least 5, or about 7-10 amino acids.

[0795] Disclosed herein are anti-PD-1 antibodies and antigen-binding fragments thereof as well as fusion proteins comprising an anti-PD1 antibody or antigen-binding fragment thereof that specifically bind to the same epitope as anti-PD-1 antibody 38B2. Also disclosed herein are anti-PD-1 antibodies and antigen-binding fragments thereof as well as fusion proteins comprising an anti-PD1 antibody or antigen-binding fragment thereof that bind to the same epitope as anti-PD-1 antibody 31B1.

[0796] As used herein, a "blocking" antibody or an antibody "antagonist" is one that inhibits or reduces the biological activity of the antigen to which it binds. For example, in some embodiments, an anti-PD-1 antagonist antibody or antigen-binding fragment thereof binds PD-1 and inhibits activity of PD-1 and/or binding of PD-1 to binding partners such as PD-L1 or PD-L2. Inhibition of activity and inhibition of binding includes partial inhibition. Methods for the identification of PD-1 antibodies that block PD-1 interactions are described herein and are known to the ones skilled in the art. For instance, competing, cross-blocking, and cross-blocked antibodies can be identified using any suitable method known in the art, including competition ELISAs or BIACORE® assays where binding of the competing or cross-blocking antibody to human PD-1 prevents the binding of an antibody disclosed herein or vice versa.

[0797] In certain embodiments, not all CDRs are directly involved in binding to the antigen. In one embodiment, four out of six CDRs of the anti-PD-1 antibody or antigen-binding fragment thereof make contact with the antigen. In one embodiment, five out of six CDRs of the anti-PD-1 antibody or antigen-binding fragment thereof make contact with the antigen. In one embodiment, six out of six CDRs of the anti-PD-1 antibody or antigen-binding fragment thereof make contact with the antigen.

[0798] The terms "selective" and "selectivity" herein refer to the preferential binding of an antibody or antigen-binding fragment thereof (i.e., a PD-1 antibody or antigen-binding fragment thereof), for a particular region, target, or peptide; typically a region or epitope in PD-1, as opposed to one or more other biological molecules, including other PD-1 family members.

[0799] In one aspect, provided are anti-PD-1 antibodies and antigen-binding fragments thereof that specifically bind to at least part of the binding site on PD-1, thereby blocking PD-1 interactions with the one or more PD-1 ligands. These PD-1 ligands include, but are not limited to, PD-L1 and PD-L2.

[0800] In certain embodiments, the anti-PD-1 antibody or antigen-binding fragments according to the disclosure comprises an Fc domain, composed of a first and a second subunit. The Fc domain of an antibody consists of a pair of polypeptide chains comprising heavy chain domains of an immunoglobulin molecule. The two subunits of the Fc domain form a stable association. In embodiments, the two subunits of the Fc domain are identical. In alternative embodiments, the two subunits of the Fc domain are non-identical. In embodiments, one subunit of the Fc domain may be fused with an immunoconjugate molecule. In embodiments, the Fc domain of the antibody may be an IgG Fc domain, an IgG1 Fc domain, an IgG2Fc domain, an IgG3 Fc domain, an IgG4 Fc domain. In a further particular embodiment, the Fc domain is a human Fc domain.

[0801] Fc Domain Modifications Promoting Heterodimerization

[0802] Further contemplated are modifications in the Fc domain of the disclosed anti-PD-1 antibodies or antigen-binding fragments thereof promoting dimerization. In embodiments, the Fc domain of the anti-PD-1 antibody or antigen-binding fragment thereof comprises a modification promoting the association of the first and the second subunit of the Fc domain. In one embodiment, said modification is in the CH3 domain of the Fc domain. In a specific embodiment, said modification promoting the association of the first and the second subunit of the Fc domain is a so-called "knob-into-hole" modification, comprising a "knob" modification in one of the two subunits of the Fc domain and a "hole" modification in the other one of the two subunits of the Fc domain.

[0803] Knob-into-hole modifications are a "protuberance-into-cavity" strategy, which serves to engineer an interface between a first and second polypeptide for hetero-oligomerization. "Protuberances" (i.e., the knobs) are constructed by replacing small amino acid side chains from the interface of the first polypeptide with larger side chains. Compensatory "cavities" (i.e., holes) of identical or similar size to the protuberances are optionally created on the interface of the second polypeptide by replacing large amino acid side chains with smaller ones. In particular embodiment, an amino acid residue in the CH3 domain of the first Fc subunit is replaced with an amino acid residue having a larger side chain volume, thereby generating a knob within the CH3 domain of the first Fc subunit which is positionable in a hole present within the CH3 domain of the second Fc subunit, generated by replacing one amino acid residue with an amino acid residue having a smaller side chain volume in the CH3 domain of the second Fc subunit. Preferably said amino acid residue having a larger side chain volume is selected from the group consisting of cysteine (C), valine (V), alanine (A), phenylalanine (F), tyrosine (Y), leucine (L), lysine (K), Proline (P), glutamic acid (E), and tryptophan (W). Preferably said amino acid residue having a smaller side chain volume is selected from the group consisting of alanine (A), serine (S), threonine (T), arginine (R), tryptophan (W), cysteine (C), lysine (L), glutamic acid (E), aspartic acid (D), and valine (V).

[0804] The mutations corresponding to the knob and the hole can be made by altering the nucleic acid encoding the polypeptides, e.g. by site-specific mutagenesis, or by peptide synthesis.

[0805] In fusion protein embodiments, which only one heavy chain is linked to IL-15/IL-15Rα sushi, the Fc domains of the anti-PD-1 antibody or antigen-binding fragment thereof may comprise one or more amino acid substitutions promoting heterodimer formation (i.e., the association the heavy chain fusion with a heavy chain lacking the fusion). In embodiments, an amino acid residue in the CH3 domain of one heavy chain (CH3-1) comprises an amino acid substitution replacing an amino acid with an amino acid residue having a larger side chain volume, thereby generating a "knob" within the CH3 domain, which is positionable in a "hole" present within the CH3 domain of the other heavy chain (CH3-2), generated by replacing an amino acid residue with an amino acid residue having a smaller side chain volume. In embodiments, the CH3 domain of the first subunit of the Fc domain (the "knobs" subunit) may comprise one or more substitution from the following; T350V, L351Y, S354C, S364H, T366Y, T366W, F405A, Y407V. In specific embodiments, the CH3 domain of the second subunit of the Fc domain (the "holes" subunit) may comprise one or more substitutions from the following; Y349C, T350V, T366L, T366S, L368A, K392L, T394W, Y407V, Y407T.

[0806] In some embodiments, the amino acid substitutions are selected from:

[0807] (1) CH3 domain of first heavy chain: S354C, T366W; CH3 domain of second heavy chain: Y349C, T366S, L368A, Y407V;

[0808] (2) CH3 domain of first heavy chain: T350V, L351Y, F405A, Y407V; CH3 domain of second heavy chain: T350V, T366L, K392L, T394W;

[0809] (3) CH3 domain of first heavy chain: L351Y, F405A, Y407V; CH3 domain of second heavy chain: T366L, K392L, T394W;

[0810] (4) CH3 domain of first heavy chain: T366W; CH3 domain of second heavy chain: Y407T;

[0811] (5) CH3 domain of first heavy chain: T366Y; CH3 domain of second heavy chain: Y407T;

[0812] (6) CH3 domain of first heavy chain: T366W; CH3 domain of second heavy chain: Y407A;

[0813] (7) CH3 domain of first heavy chain: F405A; CH3 domain of second heavy chain: T394W;

[0814] (8) CH3 domain of first heavy chain: F405W; CH3 domain of second heavy chain: T394S;

[0815] (9) CH3 domain of first heavy chain: T366Y and F405A; CH3 domain of second heavy chain: T394W and Y407T;

[0816] (10) CH3 domain of first heavy chain: T366W and F405W; CH3 domain of second heavy chain: T394S: and 407A;

[0817] (11) CH3 domain of first heavy chain: F405W and Y407A; CH3 domain of second heavy chain: T366W and T394S.

[0818] (12)

[0819] Provided herein is an antibody or antigen-binding fragment thereof, which binds to PD-1 (or a fusion protein comprising such an antibody or antigen-binding fragment thereof), wherein the antibody comprises a heavy chain comprising a sequence selected from the group consisting of SEQ ID NOS: 168-169, 171-172, 185, 191, and 201-203.

[0820] Provided herein is an antibody or antigen-binding fragment thereof (or a fusion protein comprising such an antibody or antigen-binding fragment thereof), which binds to PD-1, wherein the antibody comprises a light chain comprising a sequence selected from the group consisting of SEQ ID NOS: 170, 173, 186, 192, and 205.

[0821] In specific embodiments, the Fc domain according to the disclosure exhibits reduced binding affinity to an Fc receptor and/or reduced effector function, as compared to a native IgG1 Fc domain. In certain embodiments, the Fc domain is engineered to have reduced binding affinity to an Fc receptor and/or reduced effector function, as compared to a non-engineered Fc domain.

[0822] Linkers

[0823] In embodiments, the fusion proteins provided herein may comprise one or more linkers joining components of the fusion proteins disclosed herein. A linker may be located (i) between the IL-15 polypeptide and the IL15Rα polypeptide comprising the sushi domain; (ii) between a heavy chain of the anti-PD-1 antibody or antigen-binding fragment thereof and the IL-15 polypeptide or the IL15Rα polypeptide comprising the sushi domain; or (iii) both. In embodiments of the disclosure, the IL-15 polypeptide and the IL15Rα polypeptide comprising the sushi domain are joined or linked by a first linker amino acid sequence. In embodiments, the IL-15 polypeptide (or the IL15Rα polypeptide) is linked to an antibody, or antigen binding fragment thereof, described herein by a second linker amino acid sequence. In embodiments, the second linker joins the N terminus of the heavy chain variable region to the C terminus of the IL-15 polypeptide. The first and second linkers may have the same or different amino acid sequences.

[0824] The linker amino acids sequences described herein may be of a length sufficient to ensure that the fusion protein forms proper secondary and tertiary structures. The length of the linker amino may be between 5 to 40 amino acids, preferably 10 to 40 amino acids, more preferably 15 to 40 amino acids, still more preferably 20 to 40 amino acids, most preferably 25 to 35 amino acids.

[0825] Preferably, the linker sequences comprise near neutral amino acids selected in the group comprising Gly (G), Asn (N), Ser (S), Thr (T), Ala (A), Leu (L), and Gln (Q), most preferably in amino acids selected from the group comprising Gly (G), Asn (N), and Ser (S). Preferably, the linker sequences are glycine- and serine-rich, and in some embodiments, the linker contains only serine and glycine residues.

[0826] In some embodiments, the linker comprises a portion of the IL15Rα polypeptide outside of the sushi domain, including, but not limited to the sequence bolded in the linker of SEQ ID NO:215 (below).

[0827] Some non-limiting linker examples of amino acid sequences include

(SEQ ID NO: 215)
IRDPALVHQRPAPPSGGSGGGGSGGGSGGGGSLQ,

(SEQ ID NO: 216)
GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS;

(SEQ ID NO: 217)
IRDPSGGGGSGGGGSGGGGSGGGGSGGGGSGGGG,

-continued

(SEQ ID NO: 218)
IRDPGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS,
and

(SEQ ID NO: 244)
GGGGSGGGGSGGGGSGGGGS.

[0828] In embodiments, the linker joining the IL-15 polypeptide and the IL-15Rα sushi comprises IRDPALVHQRPAPPSGGSGGGGSGGGSGGGGSLQ (SEQ ID NO: 215), IRDPSGGGGSGGGGSGGGGSGGGGSGGGGSGGGG (SEQ ID NO: 217), or IRDPGGGGSGGGGSGG GGSGGGGSGGGGSGGGGS (SEQ ID NO:218).

[0829] In embodiments, the linker joining the IL-15 polypeptide to the anti-PD-1 antibody heavy chain comprises GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 216) or GGGGSGGGGSGGGGSGGGGS (SEQ ID NO:244).

[0830] In embodiments, the heavy and light chains of the anti-PD-1 antibody or antigen-binding fragment thereof disclosed herein may be connected into a single polypeptide chain (a "single-chain Fv" or "scFv") using a third linker that allows the VR and VL domains to associate to form an antigen-binding site. The amino acid sequence of the linkers may be the same or different.

[0831] In one embodiment, an IL-15 polypeptide or an IL-15 derivative is covalently linked to an IL-15Rα sushi polypeptide or an IL-15Rα sushi derivative by a linker.

[0832] In one embodiment, the IL-15 polypeptide or IL-15 derivative is covalently linked to an anti-PD-1 antibody or antigen-binding fragment thereof by a linker. In one embodiment, the C-terminus of the IL-15 polypeptide or IL-15 derivative is covalently linked to the N-terminus of the anti-PD-1 antibody or antigen-binding fragment thereof by a linker. In one embodiment, the N-terminus of the IL-15 polypeptide or IL-15 derivative is covalently linked to the C-terminus of the anti-PD-1 antibody or antigen-binding fragment thereof by a linker. In one embodiment, the N-terminus of the IL-15 polypeptide or IL-15 derivative is covalently linked to the CH3 region of the anti-PD-1 antibody or antigen-binding fragment thereof by a linker.

[0833] In one embodiment, the IL-15Rα sushi or an IL-15Rα sushi derivative is covalently linked to an anti-PD-1 antibody or antigen-binding fragment thereof by a linker. In one embodiment, the C-terminus of the IL-15Rα sushi polypeptide or IL-15Rα sushi derivative is covalently linked to the N-terminus of the anti-PD-1 antibody or antigen-binding fragment thereof by a linker. In one embodiment, the N-terminus of the IL-15Rα sushi polypeptide or IL-15Rα sushi derivative is covalently linked to the C-terminus of the anti-PD-1 antibody or antigen-binding fragment thereof by a linker. In one embodiment, the N-terminus of the IL-15Rα sushi polypeptide or IL-15Rα sushi derivative is covalently linked to the CH3 region of the anti-PD-1 antibody or antigen-binding fragment thereof by a linker.

[0834] In some embodiments, an IL-15 polypeptide or an IL-15 derivative is covalently linked to an IL-15Rα sushi polypeptide or a IL-15Rα sushi derivative by a first linker and either the IL-15 polypeptide or IL-15 derivative or the IL-15Rα sushi polypeptide or IL-15Rα sushi derivative is covalently linked to an anti-PD-1 antibody or antigen-binding fragment thereof by a second linker. In some embodiments, the amino acid sequences of the first and the second linker are identical. In other embodiments, the amino acid sequences of the first and the second linker are different.

[0835] Conjugates

[0836] The anti-PD-1 antibodies, antigen-binding fragments thereof, and the fusion proteins disclosed herein may further comprise one or more functional moieties. Examples of useful functional moieties include, but are not limited to, a blocking moiety, a detectable moiety, a diagnostic moiety, a targeting, and a therapeutic moiety.

[0837] A blocking moiety may include moieties of sufficient steric bulk and/or charge such that reduced glycosylation occurs, for example, by blocking the ability of a glycosidase to glycosylate the antibody or antigen-binding fragment thereof. Preferred blocking moieties include cysteine adducts such as cysteine, mixed disulfide adducts, or disulfide linkages and PEG moieties such as polyethylene glycol ("PEG"), polypropylene glycol ("PPG"), polyoxyethylated glycerol ("POG") and other polyoxyethylated polyols, polyvinyl alcohol ("PVA") and other polyalkylene oxides, polyoxyethylated sorbitol, or polyoxyethylated glucose. PEG is a preferred moiety in biological applications for several reasons. PEGylating can improve pharmacokinetic performance of a molecule by increasing the molecule's apparent molecular weight. The increased apparent molecular weight reduces the rate of clearance from the body following subcutaneous or systemic administration. In many cases, pegylation can decrease antigenicity and immunogenicity. PEGylating can also increase the solubility of a biologically active molecule. Additionally, PEG typically is clear, colorless, odorless, soluble in water, stable to heat, inert to many chemical agents, does not hydrolyze, and is nontoxic, making it a preferable choice for biological applications.

[0838] The examples of detectable moieties that can be conjugated with the anti-PD-1 antibody or the antigen-binding fragments or fusions disclosed herein may include fluorescent moieties or labels, imaging agents, radioisotopic moieties, radiopaque moieties, and the like, e.g. detectable labels such as biotin, fluorophores, chromophores, spin resonance probes, or radiolabels. Examples of fluorophores include fluorescent dyes (e.g. fluorescein, rhodamine, and the like) and other luminescent molecules (e.g. luminal). A fluorophore may be environmentally-sensitive such that its fluorescence changes if it is located close to one or more residues in the modified protein that undergo structural changes upon binding a substrate (e.g. dansyl probes). Exemplary radiolabels include small molecules containing atoms with one or more low sensitivity nuclei (13C, 15N, 2H, 125I, 123I, 99Tc, 43K, 52Fe, 67Ga, 68Ga, 111In and the like).

[0839] Diagnostic moieties include detectable moieties suitable for revealing the presence of a disease or disorder. Typically, a diagnostic moiety allows for determining the presence, absence, or levels of a molecule, for example, a target peptide, protein, or proteins, that are associated with a disease or disorder. Such diagnostics are also suitable for prognosing and/or diagnosing a disease or disorder and its progression.

[0840] Examples of therapeutic moieties include anti-inflammatory agents, anti-cancer agents, anti-neurodegenerative agents, anti-infective agents, or generally a therapeutic. The functional moiety may also have one or more of the above-mentioned functions. Exemplary therapeutic moieties may include an antibiotic, a second anti-PD-1 antibody,

or an antibody to another antigen such a tumor-specific antigen, an autoimmune tissue antigen, a virally-infected cell antigen, a Fc receptor, a T cell receptor, or a T cell co-inhibitor, or an immunotoxin, or any other therapeutic moiety useful for treating a disease or condition including cancer, autoimmune disease or chronic viral infection. Exemplary therapeutic moieties may also cytotoxin, radioactive agent, cytokine, interferon, target or reporter moiety, enzyme, toxin, peptide or therapeutic agent at any location along the molecule so long as it is able to bind its target. Examples of immunoconjugates include antibody drug conjugates and antibody-toxin fusion proteins. In certain embodiments, the antibody may be conjugated to an agent specific for a tumor cell or a virally infected cell.

[0841] A salvage receptor binding epitope as described, e.g., in U.S. Pat. No. 5,739,277 may also be attached to the antibody or antigen-binding fragment thereof (especially an antibody fragment) to increase the half-life of the antibodies or the antigen-binding fragments described herein. The term "salvage receptor binding epitope" may refer to an epitope of the Fc region of an IgG molecule (e.g., IgG1, IgG2, IgG3, or IgG4) that is responsible for increasing the in vivo serum half-life of the IgG molecule (e.g., Ghetie et al., 18 Ann. Rev. Immunol. 739 (2000).

[0842] Nucleic Acids

[0843] Also provided herein are nucleic acids encoding anti-PD-1 antibodies, antigen-binding fragments thereof and fusion proteins disclosed herein, as well as vectors, host cells, and expression systems. The term "nucleic acid" as used herein refers to a polymeric form of nucleotides of any length, either ribonucleotides or desoxyribonucleotides and includes but is not limited to, single-, double- or multi-stranded DNA or RNA, genomic DNA, cDNA, DNA-RNA hybrids, or a polymer comprising purine and pyrimidine bases, or other natural, chemically or biochemically modified, non-natural, or derivatized nucleotide bases. The nucleic acids encoding anti-PD-1 antibodies and antigen-binding fragments thereof and fusion proteins disclosed herein may be, e.g., DNA, cDNA, RNA, synthetically produced DNA or RNA, or a recombinantly produced chimeric nucleic acid molecule comprising any of those polynucleotides either alone or in combination.

[0844] The term "vector" refers to vehicle comprising a nucleic acid molecule that is capable of transporting the nucleic acid molecule into a cell. A "vector" includes, but is not limited to, a viral vector, a plasmid, a RNA vector or a linear or circular DNA or RNA molecule, which may consists of a chromosomal, non-chromosomal, semi-synthetic or synthetic nucleic acids. In some embodiments, the employed vectors are those capable of autonomous replication (episomal vector) and/or expression of nucleic acids to which they are linked (expression vectors). A number of suitable vectors are known to those of skill in the art and are commercially available.

[0845] Antibody and Fusion Protein Preparation and Expression Systems

[0846] The anti-PD-1 antibodies, antigen-binding fragments or the fusion proteins disclosed herein are typically produced by recombinant expression. Nucleic acids encoding light and heavy chain variable regions, optionally linked to constant regions, may be inserted into the same expression vectors. Alternatively, the nucleic acids encoding light and heavy chain variable regions, optionally linked to constant regions, are inserted into different expression vectors. The expression vector may further comprise one or more expression control sequences, which include, but are not limited to, promoters (e.g., homologous or heterologous promoters), signal sequences, enhancer elements, and transcription termination sequences. Preferably, the expression control sequences are eukaryotic promoter systems in vectors capable of transforming or transfecting eukaryotic host cells. Typically, the host is maintained under conditions suitable for high-level expression of the nucleotide sequences, and the collection and purification of the cross-reacting antibodies after the vector is incorporated into the appropriate host.

[0847] Commonly, expression vectors contain selection markers (e.g., ampicillin-resistance, hygromycin-resistance, tetracycline resistance or neomycin resistance) to permit detection of those cells transformed with the desired DNA sequences.

[0848] The host used to express the anti-PD-1 antibodies, antigen-binding fragments thereof or the fusion proteins disclosed herein can be a prokaryotic or eukaryotic host. Examples of suitable hosts include bacterial or eukaryotic hosts, including yeast, insects, fungi, bird and mammalian cells either in vivo, or in situ, or host cells of mammalian, insect, bird, or yeast origin. The mammalian cell or tissue can be of human, primate, hamster, rabbit, rodent, cow, pig, sheep, horse, goat, dog, or cat origin, but any other mammalian cell may be used.

[0849] Examples of bacterial hosts that can be used to express the antibodies, antigen-binding fragments or the fusion protein disclosed herein can be *E. coli*, bacilli, such as *Bacillus subtilus*, and other enterobacteriaceae, such as *Salmonella, Serratia*, and various *Pseudomonas* species.

[0850] Yeasts may also be used as hosts for expressing the express the antibodies, antigen-binding fragments or the fusion protein disclosed herein. *Saccharomyces* and *Pichia* are exemplary yeast hosts, with suitable vectors having expression control sequences (e.g., promoters), an origin of replication, termination sequences, and the like as desired. Typical promoters include 3-phosphoglycerate kinase and other glycolytic enzymes. Inducible yeast promoters include, among others, promoters from alcohol dehydrogenase, isocytochrome C, and enzymes responsible for methanol, maltose, and galactose utilization.

[0851] Mammalian cells in culture may also be used as host cells for expressing the antibodies, antigen-binding fragments or the fusion proteins disclosed herein. Examples of suitable host cell lines capable of secreting heterologous proteins (e.g., intact immunoglobulins) which are well known in the art, include CHO cell lines, various COS cell lines, HeLa cells, 293 cells, myeloma cell lines, transformed B-cells, and hybridomas. Expression vectors for these cells can include expression control sequences, such as an origin of replication, a promoter, an enhancer and necessary processing information sites such as ribosome binding site, RNA splice site and/or transcriptional terminator sequences. Examples of expression control sequences include SV40, adenovirus, bovine papilloma virus, cytomegalovirus and the like.

[0852] The anti-PD-1 antibodies, antigen-binding fragments thereof, and the fusion proteins disclosed herein can be expressed using a single expression construct or vector or multiple expression constructs or vectors (e.g., two or three expression constructs). When the antibody heavy and light chains are cloned on separate expression vectors, the vectors

are co-transfected to obtain expression and assembly of intact immunoglobulins. Once expressed, the whole antibodies, their dimers, individual light and heavy chains, or other immunoglobulin forms disclosed herein can be purified according to standard procedures of the art, including ammonium sulfate precipitation, affinity columns, column chromatography, HPLC purification, gel electrophoresis, and the like (see generally Scopes, Protein Purification (Springer-Verlag, N.Y., (1982)). Substantially pure immunoglobulins of at least about 90 to 95% homogeneity are preferred, and 98 to 99% or more homogeneity most preferred, for pharmaceutical uses.

[0853] The disclosed anti-PD-1 antibodies, antigen-binding fragments, and the fusion proteins can be made by any method known in the art. General techniques for generating human or mouse antibodies or fusion molecules are known in the art.

[0854] Methods for Modulating PD-1 Activity

[0855] In one aspect, the disclosure provides methods of using the anti-PD-1 antibodies, antigen-binding fragments thereof, and fusion proteins described herein for decreasing the interaction between PD-1 and PD-ligands, including, but not limited to, PD-L1 and PD-L2. In some embodiments, the anti-PD-1 antibody, antigen-binding fragment thereof, or fusion protein disrupts the interaction between PD-1 monomers.

[0856] The anti-PD-1 antibodies, antigen-binding fragments thereof, and fusion proteins disclosed herein are useful for reducing immunosuppression, e.g., T cell tolerance. By "reducing" is meant the ability to cause an overall decrease of about 20% or greater, 30% or greater, 40% or greater, 45% or greater, 50% or greater, of 55% or greater, of 60% or greater, of 65% or greater, of 70% or greater, or 75% or greater, 80% or greater, 85% or greater, 90% or greater, or 95% or greater, as compared to a control that is not treated. Immunosuppression can be mediated by immune inhibitory receptors expressed on the surface of an immune cell, and their interactions with their ligands. Methods of measuring T cell activity are known in the art. By way of non-limiting example, T cell tolerance can be induced by contacting T cells with recall antigen, anti-CD3 in the absence of co-stimulation, and/or ionomycin. Levels of, e.g., IL-27, LDH-A, RAB10, and/or ZAP70 (both intracellular or secreted) can be monitored, for example, to determine the extent of T cell tolerogenesis (with levels of IL-2, interferon-7 and TNF correlating with increased T cell tolerance).

[0857] The anti-PD-1 antibodies, antigen-binding fragments thereof, and fusion proteins disclosed herein are further useful for enhancing T cell expansion, activation, and proliferation.

[0858] Methods of Treatment

[0859] PD-1 μlays an important role in the immune system in regulating autoimmunity, tumor immunity, and infectious immunity. PD-1-mediated T cell inhibition is an important mechanism to prevent autoimmunity. In addition, cancer and chronic infectious diseases may usurp this regulation mechanism to drive immune suppression. Blocking PD-1 with antagonists, including monoclonal antibodies, has been studied in treatments of cancer and chronic viral infections. The ability of PD-1 to inhibit T cell activation is exploited by chronic viral infections and tumors to evade immune response. In chronic viral infections, PD-1 is highly expressed on virus-specific T cells and these T cells become "exhausted" with loss of effector functions and proliferative capacity.

[0860] PD-1 deficient animal models develop various autoimmune phenotypes including autoimmune cardiomayopathy, rheumatoid arthritis, and graft versus host disease. Specifically, they have elevated levels of IgG2b and IgA and develop mild lupus-like autoimmunity and dilated cardiomyopathy. Considering the role of PD-1 in modulating immune responses, the therapeutic agents disclosed herein that antagonize PD-1 signaling can be administered to treat diseases that involve PD-1-mediated immune suppression.

[0861] Immunomodulation is a useful therapeutic approach for treating various diseases and disorders. One approach to immunomodulation is to intervene at one or more immune checkpoints by regulators of immune activation that play a key role in maintaining immune homeostasis and preventing autoimmunity. Depending on the disease or disorder, it may be desirable to upregulate or downregulate the immune response. Tumor cells that display non-self-antigens, can evade immune attack by secreting cytokines or ligands that activate immune checkpoints. In cancer therapy, thus it is generally desirable to upregulate the immune response against tumor cells. In contrast, in treatment of autoimmune diseases, it is generally desirable to downregulate the immune response in certain tissues.

[0862] In one aspect, the disclosure provides anti-PD-1 antibodies, antigen-binding fragments thereof, and fusion proteins that are useful for treatments of subjects in need thereof.

[0863] In the methods described herein, a therapeutically effective amount of an anti-PD-1 antibody, antigen-binding fragment thereof or fusion protein disclosed herein is administered to a mammal in need thereof. The term "mammal" as used herein includes, but is not limited to, humans, laboratory animals, domestic pets, and farm animals. Preferably, the mammal is a human. "Therapeutically effective amount" as described herein refers to an amount of an anti-PD-1 antibody, antigen-binding fragment thereof or fusion protein which, when administered to a mammal, is effective in producing the desired therapeutic effect.

[0864] By "subject" is meant a mammal, including, but not limited to, a human or non-human mammal, such as a bovine, equine, canine, ovine, or feline, etc. Individuals and patients are also subjects herein.

[0865] The terms "treat," "treated," "treating," or "treatment" as used herein refer to therapeutic treatment, wherein the object is to slow down (lessen) an undesired physiological condition, disorder, or disease, or to obtain beneficial or desired clinical results. For the purposes of this disclosure, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of one or more symptoms of the condition, disorder or disease state; and remission (whether partial or total). Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. The terms "prevent," "prevention," and the like refer to acting prior to overt disease or disorder onset, to

prevent the disease or disorder from developing or to minimize the extent of the disease or disorder or slow its course of development.

[0866] In one aspect, the anti-PD-1 antibodies, antigen-binding fragments thereof and fusion proteins disclosed herein may be used to treat subjects suffering from an autoimmune disease, including but not limited to, alopecia areata, autoimmune hepatitis, celiac disease, Graves' disease, Guillain-Barre syndrome, Hashimoto's disease, hemolytic anemia, inflammatory bowel disease, inflammatory myopathies, multiple sclerosis, primary biliary cirrhosis, psoriasis, rheumatoid arthritis, scleroderma, Sjogren's syndrome, systemic lupus, erthyematosus, vitiligo, autoimmune pancreatitis, autoimmune urticaria, autoimmune thrombocytopenic purpura, Crohn's disease, diabetes type I, eosinophilic fasciitis, eosinophilic enterogastritis, Goodpasture's syndrome, myasthenia gravis, psoriatic arthritis, rheumatic fever, ulcerative colitis, vasculitis and Wegener's granulomatosis. In certain embodiments, an activating antibody disclosed herein may be used to treat a subject suffering from autoimmune disease.

[0867] In one aspect, the anti-PD-1 antibodies, antigen-binding fragments thereof and fusion proteins disclosed herein may be used to treat subjects suffering from a chronic viral infection. In a specific embodiment, the anti-PD-1 antibodies, antigen-binding fragments thereof and fusion proteins disclosed herein can be used to rescue exhausted T cells and/or decrease viral titers in a subject in need thereof. In certain embodiments, the anti-PD-1 antibodies, antigen-binding fragments thereof and fusion proteins disclosed herein may be used to treat chronic viral infection by administering a therapeutically effective dose to a subject in need thereof. In some embodiments, the subject is suffering from a viral infection caused by lymphocytic choriomeningitis virus (LCMV), human immunodeficiency virus (HIV) or human papilloma virus (HPV) or hepatitis B/C virus (HBV/HCV) or simian immunodeficiency virus (SIV).

[0868] In another aspect, the anti-PD-1 antibodies, antigen-binding fragments thereof and fusion proteins disclosed herein can be used to treat subjects suffering from primary or recurrent cancer, including, but not limited to, renal cell carcinoma, colorectal cancer, non-small-cell lung cancer, brain cancer (e.g., glioblastoma multiforme), squamous cell carcinoma of head and neck, gastric cancer, prostate cancer, ovarian cancer, kidney cancer, breast cancer, multiple myeloma, and melanoma.

[0869] In certain embodiments, anti-PD-1 antibodies, antigen-binding fragments thereof and fusion proteins disclosed herein may be administered in a therapeutically effective amount to a subject suffering from a cancer or a viral infection.

[0870] One or more anti-PD-1 antibodies, antigen-binding fragments thereof or fusion proteins disclosed herein may be administered to relieve or prevent or decrease the severity of one or more of the symptoms or conditions of the disease or disorder. In a certain embodiment, the anti-PD-1 antibodies, antigen-binding fragments thereof and fusion proteins disclosed herein may be administered prophylactically to a subject in need therefore to reduce the risk of developing a chronic viral infection or an autoimmune disease. The anti-PD-1 antibodies, antigen-binding fragments thereof and fusion proteins disclosed herein may be used as an adjunct therapy with any other agent or any other therapy known to those skilled in the art useful for treating cancer, autoimmune disease, or viral infection.

[0871] Combination Therapy

[0872] The anti-PD-1 antibodies, antigen-binding fragments thereof and fusion proteins disclosed herein may be advantageously combined with an additional therapeutic agent. Such additional agents include, but are not limited to, cytotoxic agents, chemotherapeutic agents, growth inhibitory agents, anti-inflammatory agents, anti-cancer agents, anti-neurodegenerative agents, immunosuppressive agents, and anti-infective agents. The administration of the anti-PD-1 antibody or antigen-binding fragment thereof or the fusion protein and the additional therapeutic agent may be concurrently, consecutively or intermittently. The administration of the anti-PD-1 antibody or antigen-binding fragment thereof or the fusion protein and the additional therapeutic agent may be separately or as a mixture. Further, the methods of treatment provided herein can relate to a treatment in combination with one or more therapies including but not limited to the group of antibody therapy, chemotherapy, cytokine therapy, dendritic cell therapy, gene therapy, hormone therapy, laser light therapy, and radiation therapy.

[0873] The anti-PD-1 antibodies, antigen-binding fragments thereof, and the fusion proteins of the present disclosure may be combined synergistically with one or more anti-cancer drugs or therapy used to treat cancer, including, but not limited to, renal cell carcinoma, colorectal cancer, glioblastoma multiforme, squamous cell carcinoma of head and neck, non-small-cell lung cancer, colon cancer, ovarian cancer, adenocarcinoma, prostate cancer, glioma, and melanoma. Examples of such agents include but are not limited to with an antibody to PD-L1, a second antibody to PD-1 (e.g., nivolumab), a LAG-3 inhibitor, a CTLA-4 inhibitor (e.g., ipilimumab), a TIM3 inhibitor, a BTLA inhibitor, a T IGIT inhibitor, a CD47 inhibitor, an antagonist of another T cell co-inhibitor or ligand (e.g., an antibody to CD-28, 2B4, LY108, LAI R 1, ICOS, CD1 60 or VISTA), an indoleamine-2,3-dioxygenase (IDO) inhibitor, a vascular endothelial growth factor (VEGF) antagonist [e.g., a "VEGF-Trap" such as aflibercept or other VEGF-inhibiting fusion protein as set forth in U.S. Pat. No. 7,087,411, or an anti-VEGF antibody or antigen-binding fragment thereof (e.g., bevacizumab, or ranibizumab) or a small molecule kinase inhibitor of VEGF receptor (e.g., sunitinib, sorafenib, or pazopanib)], an Ang2 inhibitor (e.g., nesvacumab), a transforming growth factor β (TGF3) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor (e.g., erlotinib, cetuximab), an agonist to a costimulatory receptor (e.g., an agonist to glucocorticoid-induced TNFR-related protein), an antibody to a tumor-specific antigen (e.g., CA9, CA1 25, melanoma-associated antigen 3 (MAGE3), carcinoembryonic antigen (CEA), antiviral drugs (e.g., zidovudine, lamivudine, abacavir, ribavirin, lopinavir, efavirenz, cobicistat, tenofovir, rilpivirine and corticosteroids), vimentin, tumor-M2-PK, prostate-specific antigen (PSA), mucin-1, MART-1, and CA1 9-9), a vaccine (e.g., Bacillus Calmette-Guerin, a cancer vaccine), an adjuvant to increase antigen presentation (e.g., granulocyte-macrophage colony stimulating factor), a bispecific antibody (e.g., CD3×CD20 bispecific antibody, PSMA×CD3 bispecific antibody), cancer vaccines (e.g., MAGE3, MUC1, EGFRv3, ALVAC-CEA), a cytotoxin, a chemotherapeutic agent (e.g., dacarbazine, temozolomide, cyclophosphamide, docetaxel, doxorubicin, daunorubicin, cisplatin, carboplatin,

gemcitabine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, and vincristine), cyclophosphamide, radiotherapy, an IL-6R inhibitor (e.g., sarilumab), an IL-4R inhibitor (e.g., dupilumab), an IL-1 0 inhibitor, a cytokine such as IL-2, IL-7, IL-21, and IL-15, an antibody-drug conjugate (ADC) (e.g., anti-CD1 9-DM4 ADC, and anti-DS6-DM4 ADC), an anti-inflammatory drug (e.g., corticosteroids, and non-steroidal anti-inflammatory drugs), a dietary supplement such as anti-oxidants or any palliative care to treat cancer, radiation therapy, and/or an antibody to a Fc receptor on immune cells for the treatment of an autoimmune disease.

[0874] Methods of Administration

[0875] The therapeutic compositions comprising any of the anti-PD-1 antibodies, antigen-binding fragments thereof or fusion proteins described herein may be administered to a subject in need thereof in any convenient manner including but not limited to by injection, transfusion, implantation or transplantation. The compositions described herein may be administered to a subject in need thereof subcutaneously, intradermally, intratumorally, intranodally, intramedullary, intramuscularly, intracranially, by intravenous or intralymphatic injection, or intraperitoneally. In one embodiment, the cell compositions of the present disclosure are preferably administered by intravenous injection.

[0876] In certain embodiments, the anti-PD-1 antibody, antigen-binding fragment thereof or the fusion protein is administered to the mammal by intravenous infusion, i.e., introduction of the anti-PD-1 antibody, antigen-binding fragment thereof or the fusion protein into the vein of a mammal over a certain period. In certain embodiments, the period is about 5 min, about 10 min, about 30 min, about 1 h, about 2 h, about 4 h, or about 8 h.

[0877] Administrative Regimens

[0878] The methods according to this aspect of the disclosure comprise sequentially administering to a subject multiple doses of an anti-PD-1 antibody, antigen-binding fragment thereof, or a fusion protein of the disclosure. As used herein, "sequentially administering," means that each dose of an anti-PD-1 antibody, antigen-binding fragment thereof, or a fusion protein of the disclosure is administered to the subject at a different point in time, e.g., on different days separated by a predetermined interval (e.g., hours, days, weeks or months). The present disclosure includes methods, which comprise sequentially administering to the patient a single initial dose of an anti-PD-1 antibody, antigen-binding fragment thereof, or a fusion protein of the disclosure, followed by one or more secondary doses of an anti-PD-1 antibody, antigen-binding fragment thereof, or a fusion protein of the disclosure, and optionally followed by one or more tertiary doses of an anti-PD-1 antibody, antigen-binding fragment thereof, or a fusion protein of the disclosure. An anti-PD-1 antibody, antigen-binding fragment thereof, or a fusion protein of the disclosure may be administered at a dose between 0.01 mg/kg to 100 mg/kg.

[0879] In certain embodiments, a dose of a compound or a composition is administered to a subject every day, every other day, every couple of days, every third day, once a week, twice a week, three times a week, once every two weeks, or once a month. In other embodiments, two, three or four doses of a compound or a composition is administered to a subject every day, every couple of days, every third day, once a week, once every two weeks or once a month. In some embodiments, a dose(s) of a compound or a composition is administered for 2 days, 3 days, 5 days, 7 days, 14 days, 21 days, or 28 days. In certain embodiments, a dose of a compound or a composition is administered for 1 month, 1.5 months, 2 months, 2.5 months, 3 months, 4 months, 5 months, 6 months or more.

[0880] Pharmaceutical Compositions

[0881] In another aspect, provided are pharmaceutically acceptable compositions that comprise a therapeutically effective amount of an anti-PD-1 antibody, antigen-binding fragment thereof, or a fusion protein of the disclosure formulated together with one or more pharmaceutically acceptable excipients.

[0882] The dosage of active agent(s) may vary, depending on the reason for use, the individual subject, and the mode of administration. The dosage may be adjusted based on the subject's weight, the age, and health of the subject, and tolerance for the compound(s) or composition.

[0883] The active agent and excipient(s) may be formulated into compositions and dosage forms according to methods known in the art. The pharmaceutical compositions provided herein may be specially formulated in solid or liquid form, including those adapted for parenteral administration, for example, by subcutaneous, intratumoral, intramuscular or intravenous injection as, for example, a sterile solution, or suspension.

[0884] Therapeutic compositions comprising anti-PD-1 antibodies or antigen-binding fragments thereof, or fusion proteins thereof may formulated with one or more pharmaceutically-acceptable excipients, which can be a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, carrier, manufacturing aid (e.g., lubricant, talc magnesium, calcium or zinc stearate, or steric acid), solvent or encapsulating material, involved in carrying or transporting the therapeutic compound for administration to the subject, bulking agent, salt, surfactant and/or a preservative. Some examples of materials which can serve as pharmaceutically-acceptable excipients include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; gelatin; talc; waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as ethylene glycol and propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents; water; isotonic saline; pH buffered solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

[0885] A bulking agent as referred herein may be described as a compound added to increase the mass of a pharmaceutical composition and to contribute to the physical structure of the formulation in the lyophilized form. Examples of bulking agent may include but is not limited to Suitable mannitol, glycine, polyethylene glycol, and sorbitol.

[0886] The therapeutic composition may optionally include a surfactant. The use of a surfactant can reduce aggregation of the reconstituted protein and/or reduce the formation of particulates in the reconstituted formulation. Examples of suitable surfactants that might be used according to the present disclosure includes but is not limited to polysorbates (e.g. polysorbates 20 or 80); poloxamers (e.g. poloxamer 188); Triton; sodium dodecyl sulfate (SDS); sodium laurel sulfate; sodium octyl glycoside; lauryl-, myri-

styl-, linoleyl-, or stearyl-sulfobetaine; lauryl-, myristyl-, linoleyl- or stearyl-sarcosine; linoleyl-, myristyl-, or cetyl-betaine; lauroamidopropyl-, cocamidopropyl-, linoleamidopropyl-, myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-betaine (e.g. lauroamidopropyl); myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-dimethylamine; sodium methyl cocoyl-, or disodium methyl oleyl-taurate; and polyethyl glycol, polypropyl glycol, and copolymers of ethylene and propylene glycol (e.g. Pluronics, PF68, etc.).

[0887] A preservative may optionally be used in the therapeutic composition described herein. Suitable preservatives for use in the formulation provided herein include octadecyldimethylbenzyl ammonium chloride, hexamethonium chloride, benzalkonium chloride (a mixture of alkylbenzyldimethylammonium chlorides in which the alkyl groups are long-chain compounds), and benzethonium chloride. Other types of preservatives include aromatic alcohols such as phenol, butyl, and benzyl alcohol, alkyl parabens such as methyl or propyl paraben, catechol, resorcinol, cyclohexanol, 3-pentanol, and m-cresol.

[0888] The therapeutic composition described herein may have a varying concentration of the anti-PD-1 antibody, antigen-binding fragment thereof, or fusion protein. For example, the compositions may comprise an anti-PD-1 antibody, antigen-binding fragment thereof or fusion protein at 10 mg/ml to 200 mg/ml, 25 mg/ml to 130 mg/ml, 50 mg/ml to 125 mg/ml, 75 mg/ml to 110 mg/ml, or 80 mg/ml to 100 mg/ml. The compositions also may comprise an anti-PD-1 antibody, antigen-binding fragment thereof or fusion protein at about 10 mg/ml, 20 mg/ml, 30 mg/ml, 40 mg/ml, 50 mg/ml, 60 mg/ml, 70 mg/ml, 80 mg/ml, 90 mg/ml, 100 mg/ml, 110 mg/ml, 120 mg/ml, 130 mg/ml, 140 mg/ml, or 150 mg/ml. In some embodiments, the therapeutic composition may be lyophilized and provided in a composition for reconstitution prior to administration.

[0889] Diagnostic Uses

[0890] The anti-PD-1 antibodies, antigen-binding fragments thereof or the fusion proteins of the present disclosure may be used to detect and/or measure PD-1 in a sample, e.g., for diagnostic purposes. The anti-PD-1 antibodies, antigen-binding fragments thereof or the fusion proteins disclosed herein may be used in an assay to detect a disease or disorder such as cancer, autoimmune disease, or chronic viral infection. Exemplary diagnostic assays for PD-1 may comprise, e.g., contacting a sample, obtained from a patient, with an anti-PD-1 antibody, antigen-binding fragment thereof, or a fusion protein of the disclosure, wherein the anti-PD-1 antibody, antigen-binding fragment thereof, or the fusion protein is labeled with a detectable label or reporter molecule or used as a capture ligand to selectively isolate PD-1 from patient samples or alternatively used in combination with a secondary antibody which is itself detectably labeled. The detectable label or reporter molecule can be a radioisotope, such as 3H, C, 32P, 35S, or 25 1; a fluorescent or chemiluminescent moiety such as fluorescein isothiocyanate, or rhodamine; or an enzyme such as alkaline phosphatase, β-galactosidase, horseradish peroxidase, or luciferase. Specific exemplary assays that can be used to detect or measure PD-1 in a sample include enzyme linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence-activated cell sorting (FACS).

[0891] Kits of the present disclosure can include any combination of agents, compositions, components, reagents, administration devices, or mechanisms, or other entities provided herein. For instance, a kit of the present disclosure may include one or more anti-PD-1 antibodies or antigen-binding fragments thereof or fusion proteins disclosed herein and one or more of a carrier composition, an administration device, and a combination therapy agent. Kits may further include a device to facilitate delivery such as syringe for injection or a tool that facilitates the delivery of therapeutic compositions to the subject in need thereof. Any of the kits provided herein can be included in a container, pack, or dispenser together with instructions for administration.

[0892] All other referenced patents and applications are incorporated herein by reference in their entirety. Furthermore, where a definition or use of a term in a reference, which is incorporated by reference herein, is inconsistent or contrary to the definition of that term provided herein, the definition of that term provided herein applies and the definition of that term in the reference does not apply.

[0893] It is to be understood that this disclosure is not limited to the particular molecules, compositions, methodologies, or protocols described, as these may vary. Any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the present disclosure. It is further to be understood that the current disclosure in this specification includes all possible combinations of such particular features. For example, where a particular feature is disclosed in the context of a particular aspect or embodiment of the disclosure herein, or a particular claim, that feature can also be used, to the extent possible, in combination with and/or in the context of other particular aspects and embodiments of the disclosure, and in the disclosure generally.

[0894] Where reference is made herein to a method comprising two or more defined steps, the defined steps can be carried out in the order as listed, or in any order or simultaneously (except where the context excludes that possibility), and the method can include one or more other steps which are carried out before any of the defined steps, between two of the defined steps, or after all the defined steps (except where the context excludes those possibilities).

[0895] To facilitate a better understanding of the present disclosure, the following examples of specific embodiments are given. The following examples should not be read to limit or define the entire scope of the disclosure.

EXAMPLES

Example 1: Identification of Anti-PD-1 Antibodies from a Distributed Bio SuperHuman 2.0 Inc. Library

[0896] hPD-1-Fc (human IgV domain fused to the N-terminal of human IgG1Fc; present as dimer in solution) or hPD-1-his (human IgV domain of PD-1 connected to the N-terminal of a six histidine peptide; present as monomer in solution) was immobilized on immuno-tubes, which were coated with an anti-his antibody or an anti-hFc antibody. Biotin-labeled hPD-1-his was captured by strepavidin-conjugated magnetic beads. The phage library was blocked with 3% PBS milk, added to the antigen-coated tubes or mixed with antigen-coated beads, and incubated at room temperature for 0.5-1 h to allow the phages to bind to the immobilized antigens. Unbound phages were washed out, while bound phages were eluted with triethlamine (pH>11). The neutralized phages were used to infect log phase *E. coli*,

which were grown at 30° C. overnight. The harvested bacteria were used to amplify the phage for the next round panning.

[0897] The heavy and light chain variable domains of selected scFv antibodies isolated from the phage library were amplified by PCR and inserted into a mammalian expression vector containing modified human IgG 1 constant domains, from which the effector functions have been removed. The full length IgG antibodies were expressed in HEK293 cells and purified by Protein A. Purified antibodies 19B6, 19B10, 23A8, 23H9, 24H9, and 23A11 (see SEQ ID NOs: 1-48, Table 25) were characterized by binding (soluble and cell expressed PD-1) and blocking assays, Biacore kinetics analysis and cytokine secretion in SEB stimulated human PBMC.

[0898] To identify higher affinity antibodies, two light chain-shuffling libraries were constructed by combining the heavy chain of lead antibody 23H9 or 24H9, respectively, with the light chain mixture from R1 panning. Higher-affinity and/or more stable variants were identified by panning in conditions that were more restricted. These matured antibodies were converted to IgG, expressed, purified, and characterized again. The higher affinity clones were expressed in CHO cells, purified by protein A and SE-HPLC to obtain higher quality to run further studies. Antibodies 31B1, 33C4, 33G8, 34C1 (see SEQ ID NOs: 49-65, Table 25) were obtained by light chain shuffling using the heavy chain of 23H9. Antibodies 32A11, 32D11, 32D2, 32G6, 38A10, 38A11, 38A4, 38A6, 38A8, 38B1, 38B10, 38B2, 38C11, 38C6, 38G11, 38G9, 38H3, 39A3, 39B11, 39B3, 39B6, 39F11, 39G5, 39G8, 39H11, 39H2, and 39H7 (see SEQ ID NOs: 66-138, Table 25) were obtained by light chain shuffling using the heavy chain of 24H9.

[0899] FIG. **1** represents the sequence alignments of exemplary antibodies generated herein. Table 25 sets forth the amino acid sequence identifiers of the heavy and light chain variable regions and CDRs of selected anti-PD-1 antibodies according to the Kabat CDR definition. The biological properties of the exemplary antibodies generated in accordance with the methods of this Example are described in detail in the Examples set forth below.

Example 2: Antibodies Isolated from Phage Display Library Bind to hPD-1

[0900] The ability of anti-hPD1 antibodies 19B6, 19B10, 23A8, 23H9, 24H9, 23A11 (isolated from HEK293 cells) to bind to hPD1 was evaluated using a dose response binding ELISA using the indicated antibodies as primary antibodies. For this, high-binding (Immulon 2HB) plates were directly coated with human PD-1-Fc (R&D, cat #1086-PD-050). Biotin labeled hPD-1-his (Sino Biologicals, cat #10377-H08H) were captured by strepavidin (Jackson 016-000-114) or anti-his antibody (R&D, cat #MAB050-100) which were coated on the plate one day before. Serial dilutions of antibodies 19B6, 19B10, 23A8, 23H9, 24H9, and 23A11 were added to antigen-coated plates and incubated at room temperature for 1-2 hs. After washing the plates with PBST (0.05%) for three times, 1/5000-1/10,000 diluted anti-hFab-HRP antibody (Jackson 109-036-097) was added to the plates, which were incubated at room temperature for about 1 h. Color was developed by adding 1:1 dilution of substrate A and B from TMB (Fisher, cat #5120-0050) followed by neutralizing with 1N H_2SO_4. OD_{450} was read using a TECAN plate reader (Table 1). The means±S.D. of the OD_{450} reading was plotted against the log antibody concentration using GraphPad Prism8. The EC_{50} value was calculated by plotting log (agonist) vs. response (three parameters) or log(agonist) vs. response-variable slope (four parameters) (FIG. **2**). The data points in FIG. **2** represent the mean±S.D. of duplicate determinations. All six antibodies exhibited similar EC_{50} and OD_{450} (10 nM) values when bound to human PD-1-Fc, but exhibited different EC_{50} and OD_{450} (10 nM) values when bound to PD-1-his (Table 1). Antibodies 23A8, 23H9, and 24H9 showed superior binding to hPD-1-his compared to the other antibodies (FIG. **2**). Three lead antibodies—23A8, 23H9 and 24H9—were selected based on their binding to PD-1-his (Table 1 and FIG. **2**).

TABLE 1

EC50 and OD at 10 nM values for binding of antibodies 19B6, 19B10, 23A8, 23H9, 24H9, and 23A11 to PD-1-Fc or PD-1-his.

		19B6	19B10	23A8	23H9	24H9	23A11
PD-1-Fc	EC50 [nM]	0.168	0.188	0.135	0.151	0.128	0.167
	OD at 10 nM	1.81 ± 0.00	1.73 ± 0.03	1.74 ± 0.00	1.75 ± 0.08	1.84 ± 0.01	2.04 ± 0.08
PD-1-his	EC50 [nM]	>100	5.34	0.523	0.350	1.31	1.00
	OD at 10 nM	0.30 ± 0.03	0.38 ± 0.01	1.15 ± 0.04	1.25 ± 0.02	0.69 ± 0.00	0.27 ± 0.02

[0901] Example 3: Antibodies isolated from phage display library block hPD-1/hPD-L1 interactions To examine the ability of anti-hPD1 antibodies 19B6, 19B10, 23A8, 23H9, 24H9, 23A11 (isolated from HEK293 cells) to block hPD-1/hPD-L1 interactions, high-binding (Immulon 2HB) plates were coated with human PD-L1-Fc (R&D, cat #156-B7-100) or PD-L2-Fc (R&D, cat #1224_PL), respectively, and blocked with 3% PBS milk. Serial dilutions of antibodies 19B6, 19B10, 23A8, 23H9, 24H9, and 23A11 were mixed with 0.5 μg/ml (final concentration) of biotin labeled hPD-1-Fc and incubated at room temperature for 1 h. The mixture was transferred to the PD-L1-Fc or PD-L2-Fc coated plate and incubated at RT for additional 1-2 h. After washing plate with PBST (0.05%) three times, 1/5000-1/10,000 diluted Strepavidin-HRP (Thermofisher, cat #21140) was added to the plates, which were incubated at room temperature for about 1 h. Color was developed by adding 1:1 dilution of substrate A and B from TMB, followed by neutralizing with 1N H_2SO_4. OD_{450} was read using a TECAN plate reader (Table 2). The means±S.D. of OD reading was plotted against the log antibody concentration using GraphPad Prism8. The EC50 value was calculated by analyzing log (agonist) vs. response (three parameters) or log(agonist) vs.—response variable slope (four parameters). The data points are the means±S.D. of duplicate determinations (FIG. **3**). All six antibodies were found to block hPD-1-Fc binding to human PD-L1 with different IC50 values (Table 2 and FIG. **3**). All six antibodies have very similar affinity to hPD-Fc. However, antibodies 23A8, 23H9 and 24H9 showed superior blocking activity to hPD-1-his compared to the other antibodies (Table 2 and FIG. **3**). The three lead clones 23A8, 23H9, and 24H9 showed >93% inhibition and >70% inhibition in the presence of 30 and 3.3 nM antibody, respectively (Table 2 and FIG. **3**).

TABLE 2

Blocking of hPD-1 to hPD-L1 by antibodies 19B6, 19B10, 23A8, 23H9, 24H9, and 23A11.

Blocking ELISA	19B6	19B10	23A8	23H9	24H9	23A11
IC50 [nM]	2.69	28.1	1.85	2.04	2.28	2.61
Inhibition % (30 nM)	85.9 ± 0.8	65.2 ± 0.6	93.1 ± 0.2	94.7 ± 0.14	92.9 ± 0.1	86.6 ± 3.0
Inhibition % (3.3 nM)	51.9 ± 2.1	22.9 ± 2.4	80.5 ± 1.0	82.5 ± 0.4	70.0 ± 1.1	54.9 ± 7.1

Example 4: Antibodies Isolated from Phage Display Library Bind to Cells Expressing Human PD-1

[0902] Binding of anti-PD-1 antibodies to HEK293 and Jurkat cells over-expressing human PD-1: Cells were cultured in IMDM medium with glutamine, supplemented with 10% heat-inactive fetal bovine serum (FBS). Cells were first incubated with the indicated anti-PD-1 antibodies, followed by incubation with an PE-anti human IgG1-Fc (R-phycoerythrin-conjugated goat anti-human IgG: Jackson ImmunoResearch cat #109-116-098). Antibody binding to hPD-1 was determined using a flow cytometry Guava EasyCyte™ HT Sampling Flow Cytometer (EMD Millipore). The data points in FIG. **4** were represent the mean±S.D. of duplicate determinations. Antibodies 23A8, 23H9, and 19B10 showed strongest binding to HEK 293 cells and antibodies 23A8, 24H9, and 19B10 showed highest mean fluorescence intensity (MFI) (Table 4 and FIG. **4**).

[0903] Binding of anti-PD-1 antibodies to SEB-activated human PBMCs: PBMCs were isolated from LeukoPak (an enriched leukapheresis containing highly concentrated blood cells including monocytes, lymphocytes, platelets, plasma, as well as red cells) using Histopaque-1077 (Sigma) using the manufacturer's instructions. PBMCs were cultured at 2×10^6/mL in a 12-well plate containing IMDM (Gibco, Life Technologies) supplemented with 10% FBS (GE Healthcare HyClone) and activated by 1 ug/mL SEB (Staphylococcal enterotoxin B, Sigma) for 3 to 4 days. Activated PBMCs were first incubated with indicated anti-PD-1 antibodies, followed by incubation with a combination of PE-anti human IgG1-Fc (R-phycoerythrin-conjugated goat anti-human IgG: Jackson ImmunoResearch cat #109-116-098) and either anti human CD4-APC (eBioscience clone RPA-T4 cat #17-0049-42) or anti human CD8-APC (eBioscience clone RPA-T8 cat #17-0088-42). Antibody binding to PD-1 expressed on cells was evaluated using a Guava EasyCyte™ HT Sampling Flow Cytometer (EMD Millipore). Data points were generated by calculating the means±S.D. of duplicate determinations (Table 3 and FIG. **4**). Antibodies 19B6, 23A8, 23H9, and 24H9 exhibited the highest MFI and lowest EC50 for binding to PBMCs among the antibodies tested and were selected for further characterization (Table 3 and FIG. **4**).

TABLE 3

Binding of indicated anti-PD-1 antibodies to (1) hPD-1-293 cells, (2) SEB-activated PBMCs from donor "EA" (low PD-1 expression), and (3) SEB-activated PBMCs from donor "AF" (high PD-1 expression).

Binding to cell-expressed PD1		19B6	19B10	23A8	23H9	24H9	23A11
hPD1-293	EC50 [nM]	Very low	16.0	0.299	2.53	58.7	Very low
	MFI at 68 nM	20.84 ± 0.48	45.07 ± 0.0	104.85 ± 1.68	38.84 ± 4.03	59.04 ± 6.30	21.77 ± 0.16
SEB activated PBMC, donor EA	EC50 [nM]	13.6	117	1.51	0.993	1.37	19.0
	MFI at 100 nM	13.74 ± 0.05	12.41	19.88 ± 0.28	26.19 ± 0.18	18.71 ± 0.24	14.58 ± 0.01
SEB activated PBMC, donor AF	EC50 [nM]	10.7	104	1.89	0.829	0.913	13.4
	MFI at 100 nM	51.23 ± 1.73	25.19 ± 0.15	80.29 ± 1.33	108.59 ± 5.01	70.52 ± 3.74	46.19 ± 1.18

Example 5: Antibodies Isolated from Phage Display Library Disrupt Intercellular PD-1/PD-L1 Interactions

[0904] To assess the ability of selected anti-PD-1 antibodies to disrupt the binding of PD-1 expressing cells to PD-L1 expressing cells, the Promega PD-1/PD-L1 Blockade Bioassay was used. This assay consists of two genetically engineered cell lines, PD-1 effector cells and PD-L1 aAPC/CHO-K1 cells. When co-cultured, the PD-1/PD-L1 interaction inhibits TCR-mediated luminescence. When the PD-1/PD-L1 interaction is disrupted, TCR activation induces luminescence (via activation of the NFAT pathway) that can be detected by addition of Bio-Glo™ Reagent and quantitation with a luminometer.

The experiment was performed according to the manufacturer's instructions. Briefly, PD-L1 aAPC/CHO-K1 cells were plated and incubated for 16-20 h prior to the addition of increasing concentrations of anti-PD-1 antibodies and PD-1 effector cells. After 6 h of incubation at 37° C., Bio-Glo™ Reagent was added and luminescence (recorded as relative light unites, RLU) was measured by using a TECAN plate reader. Fold induction was calculated by RLU (induced-background)/RLU (no antibody control-background). Data points are represented as means±S.D. of

duplicate determinations (FIG. **5**). Antibodies 19B6, 23A8, 23H9 and 24H9 blocked hPD-1/hPD-L1 interaction with different EC50s and fold induction (Table 4 and FIG. **5**).

TABLE 4

Blocking of hPD-1/hPD-L1 interactions by antibodies 19B6, 23A8, 23H9, and 24H9.

	23A8	23H9	24H9	19B6
EC 50, μg/mL	4.73	0.688	0.823	2.127
Fold of induction	2.81 ± 0.16	4.42 ± 0.11	3.96 ± 0.12	3.04 ± 0.29

[0905] Antibodies 23H9 and 24H9 were selected for light chain shuffling, wherein the heavy chains of 23H9 or 24H9, respectively, were paired with a library of light chains. Antibodies 31B1, 33C4, 33G8, 34C1 (see SEQ ID NOs: 49-65, Table 25) were obtained by light chain shuffling using the heavy chain of 23H9. Antibodies 32A11, 32D11, 32D2, 32G6, 38A10, 38A1i, 38A4, 38A6, 38A8, 38B1, 38B10, 38B2, 38C11, 38C6, 38G11, 38G9, 38H3, 39A3, 39B11, 39B3, 39B6, 39F11, 39G5, 39G8, 39H11, 39H2, and 39H7 (see SEQ ID NOs: 66-138, Table 25 were obtained by light chain shuffling using the heavy chain of 24H9.

Example 6: Anti-hPD-1 Antibody 23H9 and its Derivatives Bind to hPD-1 and Block hPD-1/hPD-L1 Interactions

[0906] The ability of anti-hPD1 antibody 23H9 and its derivatives 31B1, 33C4, 33G8, and 34C1 to bind to hPD1 and to block hPD-1/hPD-L1 interactions was determined using the protocols described in Examples 2 and 3, respectively. The parental antibody 23H9 and its derivatives showed no significant difference in binding to hPD-1-Fc and biotin-hPD-1-his captured by strepavidin (Table 5 and FIG. **6**A). However, all derivatives were more potent than their parental 23H9 in binding to the anti-his captured hPD-1-his and in blocking interactions of hPD-1-F/hPD-L1-Fc (Table 5 and FIG. **6**B). Two clones (31B1 and 33C4) were selected for further characterization (Table 5).

TABLE 5

Binding of antibodies 23H9, 31B1, 33C4, 33G8, and 34C1 to hPD-1-Fc, binding to strepavidin-captured biotin-hPD-1-his, binding to ahis-captured hPD-1-his, and blocking of hPD-1-Fc/hPD-L1-Fc interaction.

Binding/blocking ELISA		23H9	31B1	33C4	−34C1	33G8
Binding hPD1-Fc	EC50, nM	0.121	0.167	0.177	0.147	0.113
	OD450 at 10 nM	0.916 ± 0.045	0.974 ± 0.082	0.925 ± 0.009	0.926 ± 0.045	0.900 ± 0.006
Biotin-hPD-1-his captured by Strep	EC50, nM	0.18	0.244	0.209	0.233	0.197
	OD450 at 10 nM	0.890 ± 0.004	0.953 ± 0.006	0.950 ± 0.069	0.945 ± 0.014	0.909 ± 0.028
hPD-1-his captured by anti-his	EC50, nM	0.238	0.095	0.061	0.0866	0.149
	OD450 at 10 nM	0.406 ± 0.024	0.590 ± 0.026	0.578 ± 0.015	0.521 ± 0.009	0.487 ± 0.040
Blocking PD1/PD-L1	IC50, nM	1.27	2.15	2.06	2.01	1.81
	Inhibition % at 50 nM	90.4 ± 0.3	91.4 ± 0.2	92.5 ± 0.0	89.3 ± 0.1	90.5 ± 0.2
	Inhibition % at 5.6 nM	88.6 ± 0.5	90.2 ± 0.3	91.2 ± 0.2	89.1 ± 0.1	89.9 ± 1.2

Example 7: Anti-hPD-1 Antibody 24H9 and its Derivatives Bind to hPD-1 and Block hPD-1/hPD-L1 Interactions

[0907] The ability of anti-hPD1 antibody 24H9 and its derivatives 32A11, 32D2, 32D11, 38A6, 38A10, 38A11, 38B2, 38C11, 39B3, 39B11, 39G8 and 38H11 to bind to hPD1 and to block hPD-1/hPD-L1 interactions was determined using the protocols described in Examples 2 and 3, respectively. The parental antibody 24H9 and its derivatives showed no significant difference in binding to hPD-1-Fc and hPD-A-his captured by strepavidin (FIG. **7**). However, all derivatives were found to be more potent than parental 24H9 in binding to the anti-his captured hPD-1-his and blocking interaction of hPD-1-Fc-hPD-L1-Fc (FIG. **7**).

[0908] Two clones (38A6 and 38D2) were picked for further characterization (Table 6).

Example 7: Anti-hPD-1 Antibody 24H9 and its Derivatives Bind to hPD-1 and Block hPD-1/hPD-L1 Interactions

[0907] The ability of anti-hPD1 antibody 24H9 and its derivatives 32A11, 32D2, 32D11, 38A6, 38A10, 38A11, 38B2, 38C11, 39B3, 39B11, 39G8 and 38H11 to bind to hPD1 and to block hPD-1/hPD-L1 interactions was determined using the protocols described in Examples 2 and 3, respectively. The parental antibody 24H9 and its derivatives showed no significant difference in binding to hPD-1-Fc and hPD-A-his captured by strepavidin (FIG. **7**). However, all derivatives were found to be more potent than parental 24H9 in binding to the anti-his captured hPD-1-his and blocking interaction of hPD-1-Fc-hPD-L1-Fc (FIG. **7**).

[0908] Two clones (38A6 and 38D2) were picked for further characterization (Table 6).

TABLE 6

Binding of antibodies 24H9, 32A11, 32D2, 32D11, 38A6, 38A10, 38A11, 38B2, 38C11, 39B3, 39B11, 39G8 and 38H11 to hPD-1-Fc, binding to strepavidin-captured hPD-1-his, binding to ahis captured hPD-1-his, and blocking of hPD-1/hPD-L1 interaction.

	hPD-1-Fc		Strep captured PD-1-his		Anti-his captured PD-1-his		Blocking	
Name	EC50	OD at 10 nM	EC50	OD at 10 nM	EC50	OD at 10 nM	IC50	Inhibition at 50 nM
24H9	0.117	0.982 ± 0.007	0.206	0.915 ± 0.019	0.738	0.207 ± 0.006	3.073	87.4 ± 0.5
32A11	0.109	0.921 ± 0.003	0.21	0.919 ± 0.005	0.221	1.035 ± 0.003	2.639	91.1 ± 0.0
32D2	0.084	0.922 ± 0.027	0.203	0.932 ± 0.027	0.216	0.591 ± 0.010	2.581	91.7 ± 0.1
32D11	0.114	0.952 ± 0.039	0.177	0.935 ± 0.004	0.229	0.602 ± 0.013	2.418	91.9 ± 0.1
38A6	0.102	0.993 ± 0.004	0.175	0.948 ± 0.013	0.217	0.576 ± 0.001	2.183	91.7 ± 0.2
24H9	0.11	1.050 ± 0.018	0.272	0.994 ± 0.035	0.043	0.267 ± 0.028	2.535	86.8 ± 0.4
38A10	0.112	1.057 ± 0.025	0.19	1.003 ± 0.088	0.117	0.552 ± 0.002	2.402	92.8 ± 1.1
38A11	0.089	1.033 ± 0.014	0.204	1.069 ± 0.002	0.157	0.447 ± 0.056	2.088	93.2 ± 0.1
38B2	0.079	1.051 ± 0.004	0.145	1.044 ± 0.011	0.076	0.662 ± 0.053	1.63	93.4 ± 0.0
38C11	0.104	1.020 ± 0.024	0.293	1.049 ± 0.019	0.229	0.404 ± 0.024	2.384	92.7 ± 0.0
24H9	0.171	1.092 ± 0.010	0.336	0.971 ± 0.013	0.797	0.165 ± 0.034	2.698	86.5 ± 0.3
39B3	0.179	1.079 ± 0.009	0.264	0.963 ± 0.008	5.013	0.617 ± 0.061	2.315	92.9 ± 0.1
39B11	0.116	1.082 ± 0.011	0.234	0.990 ± 0.001	23.98	0.482 ± 0.014	2.023	93.3 ± 0.0
39G8	0.099	1.063 ± 0.019	0.224	0.981 ± 0.019	4.982	0.484 ± 0.006	1.732	93.2 ± 0.0
38H11	0.115	1.083 ± 0.018	0.235	0.956 ± 0.014	2.146	0.699 ± 0.022	2.05	93.6 ± 0.1

Example 8: The Binding Profile of 23H9 and 24H9 Derivatives Indicate that these Antibodies Bind to Different Binding Epitopes

[0909] Dose response binding assay using 23H9, 31B1, 33C4, 24H9, 38A6, and 38B2 were performed according to the protocol disclosed in Example 4. The results are shown in FIG. **8**. 23H9 derivatives and 24H9 derivatives were found to be more potent in binding to PD-1 expressing cells than their parental antibodies (Table 7). Further, 23H9 derivatives and 24H9 derivatives showed different binding profiles, indicating indicated they bind to different binding epitopes (FIG. **8**).

TABLE 7

Binding of indicated antibodies to hPD-1-293 and hPD-1 Jurkat, and SEB-activated PBMC from donor "FA" and "FB".

		23H9	31B1	33C4	24H9	38A6	38B2
hPD1-293	EC50, nM	0.33	0.077	0.075	2.69	0.15	0.12
	MFI at 5 nM	43.01	46.4 ± 0.2	48.2 ± 1.6	42.79	110.3 ± 2.5	118.3 ± 0.3
hPD1-Jurkat	EC50, nM	0.42	0.084	0.084	0.77	0.21	0.16
	MFI at 5 nM	119.6	91.6 ± 6.7	98.3 ± 7.5	80.6	89.5 ± 3.9	91.0 ± 0.0
Activated PBMC-(FA)	EC50, nM	NA	0.049	0.041	NA	0.21	0.15
	MFI at 25 nM	NA	18.4 ± 0.6	17.6 ± 0.2	NA	14.5 ± 0.0	16.6 ± 0.2

TABLE 7-continued

Binding of indicated antibodies to hPD-1-293 and hPD-1 Jurkat, and SEB-activated PBMC from donor "FA" and "FB".

		23H9	31B1	33C4	24H9	38A6	38B2
Activated PBMC-(FB)	EC50, nM	NA	0.025	0.050	NA	0.17	0.10
	MFI at 25 nM	NA	17.8 ± 0.3	18.7 ± 0.4	NA	15.9 ± 0.5	16.7 ± 1.7

Example 9: Antibodies 23H9, 24H9 and their Derivatives Disrupt Intercellular PD-1/PD-L1 Interactions

[0910] A PD-1 blockade bioassay was performed using antibodies 23H9, 31B1, 33C4, 24H9, 38A6, and 38B2 according to the protocol outlined in Example 5. All derivatives were found to be more potent than their parental antibody 23H9 and 24H9 in blocking hPD-1-hPD-L1 interactions (FIG. **9**). 38B2 and 31B1 were found to show lowest EC50 and maximum fold induction among the six antibodies tested (Table 8 and FIG. **9**).

TABLE 8

Blocking of PD-1/PD-L1 interactions by antibodies 23H9, 31B1, 33C4 and 24H9, 38B2, and 38A6 using a Promega binding assay.

	23H9	31B1	33C4	24H9	38A6	38B2
EC50, μg/ml	0.551	0.139	0.165	0.855	0.164	0.154
Fold induction	5.58 ± 0.28	6.48 ± 0.035	6.24 ± 0.092	4.97 ± 0.049	5.66 ± 0.636	6.54 ± 0.071

Example 10: The Effect of Anti-PD-1 Antibodies on Cytokine Production in SEB-Activated PBMCs

[0911] The effect of anti-PD-1 antibodies on cytokine production using 38A6, 38B2, 31B1, and 33C4 in SEB activated PBMC from donor FA was assessed by measuring the amount of cytokines released by PBMCs in the culture medium. PBMCs were isolated from LeukoPak (an enriched leukapheresis containing highly concentrated blood cells including monocytes, lymphocytes, platelets, plasma, as well as red cells) using Histopaque-1077 (Sigma) per manufacture instruction. PBMCs were cultured at 1×10^5 per well in 96 well plate containing IMDM (Gibco, Life Technologies) supplemented with 10% FBS (GE Healthcare HyClone). The cells were activated by 0.01 ug/mL SEB (Staphylococcal enterotoxin B, Sigma) for 2 days. Supernatants were collected for the measurement of IL-2 using Duoset ELISA Kit (R&D Systems) per the manufacturer's instructions (FIG. **10**A).

[0912] The experiment was repeated to obtain EC50 values for antibodies 23H9, 31B1, 24H9, and 38B2 using PBMCs from donor EA (FIG. **10**B).

[0913] IL-2 concentration increased in the presence of all antibodies in a dose-dependent manner (FIGS. **10**A, **10**B). IL-2 concentrations increased in presence of 23H9 derivative 31B1 and 24H9 derivative 38B2, which were found to be more potent than their parental antibody 23H9 and 24H9, respectively (Table 9 and FIG. **10**B).

TABLE 9

IL-2 accumulation for PBMCs from donor EAand respective EC50 and IL-2 accumulation data in presence of antibodies 23H9, 31B1, 24H9, and 38B2.

	23H9	31B1	24H9	38B2
EC 50, nM	0.344	0.107	>10	0.019
IL-2, pg/ml in 10 nM	3931 ± 52	5809 ± 90	4476 ± 35	4995 ± 140

Example 11: Biacore Analysis of Selected 23H9 and 24H9 Derivatives

[0914] The binding kinetics of the antibodies to either hPD-1-Fc or hPD-1-his was measured by surface plasmon resonance (SPR) using the Biacore T200. Human PD-1-Fc or PD-1-his protein was immobilized at pH5 onto a Series S CM5 sensor chip using standard amine coupling chemistry. Antibodies 23H9 and 23H9 derivatives 31B1, 33C4 as well as 24H9 and 24H9 derivatives 38A6, 38B2, 32D11, 39G8, 38A10, and 38A11 were injected at 30 μl/min at concentrations ranging from 1.5 to 100 nM over the immobilized surface using 1×HBSEP as the running buffer. The contact time (association phase) was 3 mins. The dissociation time was 6-10 mins. Regeneration was performed after each binding cycle with an injection of 20 mM HCl for 30 sat 30 μl/min flow rate. Sensorgrams were obtained at each concentration and the derived curves were fit to a 1:1 Langmuir binding model using Biaevaluation software. Derivative 31B1 and 33C4 were found to be more potent than the parental 23H9 in their binding to hPD-1-Fc (Table 10). All derivatives of 24H9 were found to be more potent than the parental antibody 24H9 in their binding to hPD-1-his and hPD-1-Fc.

TABLE 10

hPD1 binding characteristics of indicated antibodies as determined by SPR analysis.

	hPD1his			hPD1Fc		
Antibody	k_a	k_d	K_D	k_a	k_d	K_D
24H9	1.64 E+05	2.27 E−03	1.39 E−08	3.97 E+05	5.81 E−04	1.46 E−09
38B2	1.26 E+05	4.01 E−05	3.1S E−10	9.40 E+05	2.34 E−04	2.49 E−10
38A6	4.72 E+05	5.59 E−04	1.18 E−09	2.01 E+05	9.57 E−05	4.77 E−10
32D11	1.67 E+05	2.41 E−04	1.44 E−09	1.54 E+05	8.52 E−05	5.54 E−10
39G8	1.81 E+05	4.67 E−04	2.58 E−09	2.15 E+05	1.71 E−04	7.94 E−10
38A10	1.12 E+05	5.41 E−04	4.82 E−09	2.06 E+05	1.72 E−04	8.34 E−10
38A11	1.07 E+05	5.25 E−04	4.93 E−09	2.20 E+05	2.25 E−04	1.02 E−09
Antibody	hPD1his k_a	hPD1Fc k_d	hPD1his K_D	hPD1Fc k_a	hPD1his k_d	hPD1Fc K_D
23H9	8.64 E+04	4.24 E−04	4.91 E−09	1.69 E+05	1.57 E−04	9.28 E−10
31B1	2.78 E+05	1.82 E−03	6.56 E−09	3.44 E+05	2.37 E−04	6.88 E−10
33C4	9.43 E+04	6.35 E−04	6.73 E−09	2.77 E+05	1.60 E−04	5.75 E−10

Example 12: Thermo-Stability Measurement of Selected 23H9 and 24H9 Derivatives by Differential Scanning Calorimeter (DSC)

[0915] Selected 23H9 and 24H9 derivatives, 31B1, 33C4, 38A6, and 38B2 were cloned and expressed by WuXi Biologics by using WuXi's mammalian expression vector and CHO knockout cell line. All antibodies were purified using protein A and SEC-HPLC. More than 2.5 mg of purified antibody was obtained from 20 ml culture after Protein A and SEC-HPLC purification. The monomer percentage of all antibodies was over 96% with endotoxin levels lower than 1.0 EU/mg. Differential scanning calorimetry (DSC) was used to determine the stability of the four antibodies. The DSC analysis was performed using a Malven DSC system. The protein sample was first diluted to 1 mg/mL with formulation buffer before analysis. 400 μl respective formulation buffer was added to a 96-well plate as reference and 400 μL protein sample was added. The samples were heated from 10° C. to 100° C. at a heating rate of 90° C./h in the capillary DSC system. The DSC results (T_m onset and T_m values) were analyzed using the vendor's software. The lowest thermal transition midpoint (T_{m1}) of 31B1, 33C4, 38A6, and 38B2 were 70.5, 74.0, 71.0, and 71.9° C. respectively (FIG. **11**A). The monomer percentage of all antibodies was over 96% with Endotoxin level lower than 1.0 EU/mg (Table 11). 33C4 and 38B2 were found to be most thermostable of all the antibodies tested (Table 11).

TABLE 11

Thermo-stability measurement for antibodies 31B1, 33C4, 38A6, and 38B2 as determined by differential scanning calorimeter (DSC) and antibody monomer percentage after SEC-HPLC purification.

	Protein A		SEC HPLC						Endotoxin
	Amount	Purity,	Amount	Purity,	DSC (° C.)				(EU/mg,
Name	(mg)	%	(mg)	%	$T_{m\ on}$	T_{m1}	T_{m2}	T_{m3}	LAL)
780 38 (31B1)	4.70	97.2	2.44	96.1	60.8	70.5	74.0	83.7	<1.0
780 39 (33C4)	4.10	95.8	2.43	96.9	62.1	74.0	83.8	ND	<1.0
780 46 (38A6)	7.95	94.6	5.22	98.7	62.8	71.0	77.6	84.9	<1.0
780 54 (38B2)	7.24	95.6	5.24	99.3	62.6	71.9	84.0	ND	<1.0

Example 13: Selected 23H9 and 24H9 Derivatives Bind to hPD-1 and Block hPD-1/hPD-L1 as Well as hPD-1/hPD-L2 Interactions

[0916] Binding and Blocking ELISA were performed using antibodies 31B1, 33C4, 38A6, 38B2 isolated from transient CHOk cells using the protocols outlined in Examples 2 and 3, respectively. Comparison of the antibodies using binding ELISA showed no significant differences among the derivatives in binding to hPD-1-Fc, strepavidin-captured biotin-labeled hPD-1his and anti-his antibody captured hPD-1-his directly bound to the plates (FIG. **12**A-C). However, EC50s of 38B2 and 38A6 (both 24H9 derivatives) were lower than 31B2 and 33C4 (both 23H9 derivatives) and were superior to both controls (Table 12 and FIG. **12**A-C).

[0917] Comparison of the antibodies using blocking ELISAs showed no significant differences among the derivatives in blocking hPD-1/hPD-1 and hPD-1/hPD-L2 interactions (FIG. **12**D-E). However, similar to binding ELISA, antibodies 38A6 and 38B2 (both 24H9 derivatives) were found to be more potent than 31B2 and 33C4 (both 23H9 derivatives), especially for the inhibition of hPD-L2 binding to hPD-1 (Table 13 and FIG. **12**D-E).

TABLE 12

Binding of antibodies 31B1, 33C4, 38B2, and 38A6 to hPD-1FC, streptavidin-captured biotin-labeled hPD-lhis, and anti-his antibody captured hPD-1his.

Ec50 nM	ctB	ctM	31B1	33C4	38A6	38B2
PD-1-Fc	0.102	0.166	0.114	0.128	0.079	0.096
strep/Bio-PD-1-his	0.084	0.15	0.104	0.131	0.084	0.081
anti-his/PD-1h-is	0.094	0.105	0.139	0.142	0.089	0.060

ctB = control B (Nivolumab, sold under the brand name Opdivo).

ctM = control M (Pembrolizumab, sold under the brand name Keytruda).

TABLE 13

Ability of indicated antibodies to block hPD-1-hPD-L1 and hPD-1-hPD-L2 interactions.

	Blocking		ctB	ctM	31b1	33C4	38A6	38B2
PD-L1/PD-1	IC50, nM		1.811	2.024	2.65	2.77	~2.14	2.37
	Inhibition, %	50 nM	93.4 ± 0.3	93.1 ± 0.5	9.28 ± 0.3	93.3 ± 0.1	92.2 ± 0.0	93.9 ± 0.1
		5.56 nM	92.3 ± 0.4	90.3 ± 0.22	89.7 ± 0.1	88.9 ± 0.4	92.0 ± 0.8	92.7 ± 0.6

TABLE 13-continued

Ability of indicated antibodies to block hPD-1-hPD-L1 and hPD-1-hPD-L2 interactions.

	Blocking		ctB	ctM	31b1	33C4	38A6	38B2
PD-L2/PD-1	IC50, nM		2.222	2.749	3.94	3.3	2.39	1.93
	Inhibition, %	100 nM	93.8 ± 0.1	94.8 ± 0.1	94.5 ± 0.1	94.6 ± 0.3	94.8 ± 0.1	95.1 ± 0.0
		3.7 nM	88.6 ± 0.3	85.8 ± 4.0	41.4 ± 0.3	53.4 ± 5.7	90.4 ± 0.8	93.9 ± 0.3

ctB = control B (Nivolumab, sold under the brand name Opdivo).

ctM = control M (Pembrolizumab, sold under the brand name Keytruda).

Example 14: Dose-Response Binding Assay Using 33B1, 33C4, 38A6, and 38B2

[0918] Dose response binding assays were performed using antibodies 33B1, 33C4 (both 23H9 derivatives), 38A6 and 38B2 (both 24H9 derivatives) using the protocols outlined in Example 4.

[0919] Dose-response binding assays showed no difference between the two derivatives from the same parental antibody in binding of the antibodies to hPD-1 transfected HEK-293 and Jurkat cells, and SEB-activated PBMCs (Table 14 and FIG. **13**). However, the derivatives derived from different parental antibodies showed differences of binding to different cell lines, suggesting that 23H9 derivatives and 24H9 derivatives have different binding epitopes (Table 14 and FIG. **13**).

TABLE 14

Dose-response binding of antibodies 31B1, 33C4, 38A6, and 38B2 to hPD-1-293 cells, hPD-1-Jurkat cells, SEB-activated PBMCs from donor FA, and SEB-activated PBMCs from donor FB.

	ctB		ctM		31B1	
Cell line	EC50	MFI, 5 nM	EC50	MFI, 5 nM	EC50	MFI, 5 nM
hPD-1-Jurkat cells	0.101	64.4 ± 1.2	0.085	58.8 ± 3.1	0.100	67.0 ± 2.1
hPD-1-293 cells	0.156	195.1 ± 15.7	0.141	223.4 ± 10.0	0.229	186 ± 2
SEB activated PBMC, donor FA	0.084	61.6 ± 8.1	0.082	78.6 ± 5.73	0.136	98.5 ± 10.1
SEB activated PBMC, donor FB	0.151	55.5 ± 4.9	0.102	50.6 ± 0.8	0.209	67.7 ± 0.2

TABLE 14-continued

Dose-response binding of antibodies 31B1, 33C4, 38A6, and 38B2 to hPD-1-293 cells, hPD-1-Jurkat cells, SEB-activated PBMCs from donor FA, and SEB-activated PBMCs from donor FB.

	33C4		38A6		38B2	
Cell line	EC50	MFI, 5 nM	EC50	MFI, 5 nM	EC50	MFI, 5 nM
hPD-1-Jurkat cells	0.115	65.2 ± 0.8	0.451	59.9 ± 1.3	0.362	60.8 ± 3.4
hPD-1-293 cells	0.213	179 ± 7	0.211	227 ± 6	0.239	297 ± 2
SEB-activated PBMCs, donor FA	0.080	77.8 ± 2.4	0.206	65.2 ± 1.0	0.224	64.2 ± 2.7
SEB-activated PBMCs, donor FB	0.174	66.9 ± 0.1	0.387	54.7 ± 2.9	0.287	55.3 ± 5.4

ctB = control B (Nivolumab, sold under the brand name Opdivo).

ctM = control M (Pembrolizumab, sold under the brand name Keytruda).

Example 15: Selected 23H9 and 24H9 Derivatives Bind to hPD-1 with High Affinity

[0920] Binding of selected antibodies to hPD-1 his and hPD-1Fc was determined by SPR. Biacore analysis of 31B1, 33C4, 38A6, and 38B2 was performed using the protocol described in Example 11. All four antibodies were found to have high affinity to both hPD-1-Fc and hPD-1-his (Table 15 and FIG. **14**). However, between two derivatives of 23H9, 3 3B1 was found to be more potent than 33C4 in both binding to PD-1-Fc and PD-1-his (Table 15). Between two derivatives of 24H9, 38B2 was found to be slightly more potent than 38A6 in binding to hPD-1-Fc and showed no significant difference in binding to hPD-1-his. Both 31B1 and 38B2 were found to be superior to the two controls (Table 15).

TABLE 15

Binding of antibodies 38B2, 38A6, 33C4, and 31B1 to hPD-1 his and hPD-1Fc as determined by SPR.

	KD, nM (Exp. 1)		KD, nM (Exp. 2)		KD, nM (Exp. 3)		KD, nM (Exp. 4)		Kp range, nM	
Name	hpD1-his	hPD1-Fc	hpD1-his	hPD1-Fc	hpD1-his	hPD1-Fc	hpD1-his	hPD1-Fc	hPD1-his	hPD1-Fc
ctB	2.16	0.188	<0.857	<0.166	<1.39	<0.255	0.914	NA	0.86-2.16	0.17-0.26
ctM	3.51	0.225	<1.39	<0.345	<1.39	<0.322	1.32	NA	1.32-3.51	0.23-0.35
31B1	<0.036	<0.014	<0.01	NA	0.353	<0.01	<0.019	NA	0.01-0.35	0.01-0.02
33C4	0.704	<0.022	0.205	<0.01	0.274	<0.01	<0.054	NA	0.05-0.70	0.01-0.02
38A6	2.3	<0.188	<0.586	<0.136	<0.574	<0.301	<0.090	NA	0.09-2.30	0.14-0.30
38B2	0.946	<0.033	0.423	<0.01	0.932	<0.01	0.205	NA	0.21-0.95	0.01-0.03

ctB = control B (Nivolumab, sold under the brand name Opdivo).

ctM = control M (Pembrolizumab, sold under the brand name Keytruda).

Example 16: Antibodies 31B1 and 38B2 Disrupt Intercellular PD-1/PD-L1 Interactions 31B1 and 38B2

[0921] To assess the ability of 31B1 and 38B2 to disrupt the binding of PD-1 expressing cells to PD-L1 expressing cells, Promega PD-1/PD-L1 Blockade Bioassays were performed using the protocol described in Example 5. No significant difference was observed in EC50 and fold induction between 31B1 and 38B2 (FIG. **15**). Both 31B1 and 38B2 were found to be superior to control B (Nivolumab, sold under the brand name Opdivo) and similar to control M (Pembrolizumab, sold under the brand name Keytruda) (Table 16).

TABLE 16

Ability of antibodies 31B1 and 38B2 to blockintercellular hPD-1-hPD-L1 interactions.

	31B1		38B2		ctM	ctB
Reading, 10 mins	Exp. 1	Exp. 2	Exp. 1	Exp. 2	Exp. 1	Exp. 2
EC50, μg/ml	0.168	0.172	0.189	0.135	0.109	0.187
Fold induction at 12 μg/ml	7.44 ± 0.18	8.40 ± 0.46	7.61 ± 0.15	8.31 ± 0.58	7.40 ± 0.31	6.86 ± 0.16

ctB = control B (Nivolumab, sold under the brand name Opdivo).
ctM = control M (Pembrolizumab, sold under the brand name Keytruda).

Example 17: The Effect of 31B1 and 38B2 on Cytokine Production in SEB Activated PBMC

[0922] The effect of 31B1 and 38B2 on cytokine production in SEB-activated PBMCs was determined using the protocol outlined in Example 4. 38B2 was found to be more potent than 31B1 and the two control antibodies tested (Table 17 and FIG. **16**).

TABLE 17

Effect of PD-1 antibodies 31B1 and 38B2 on IL-2 cytokine production in SEB-activated PBMC from donor EA and FA.

	ctM	ctB	31B1		38B2	
Name	Donor EA	Donor EA	Donor EA	Donor FA	Donor EA	Donor FA
EC50, nM	0.210	0.548	0.297	1.362	0.101	0.070
IL-2 (ng/mL) at 10 nM	7.21 ± 0.35	6.79 ± 0.64	7.79 ± 0.26	11.72 ± 2.8	7.77 ± 0.13	14.14 ± 0.37
IL-2 (ng/ml) at 2.5 nM	7.25 ± 0.08	6.31 ± 0.05	7.73 ± 0.03	12.16 ± 0.00	8.05 ± 0.29	13.80 ± 0.75

ctB = control B (Nivolumab, sold under the brand name Opdivo).
ctM = control M (Pembrolizumab, sold under the brand name Keytruda).

Example 18: Isolation of Antibodies that Cross-React with Human and Mouse from Distributed Bio SuperHuman 2.0 Inc. Library

[0923] PD-1 antibodies that bind to both murine and human PD-1 were isolated using mPD-1-Fc (mouse IgV domain to fuse to the N-terminus of human IgG1Fc; present as dimer in solution) or mPD-1-his (mouse IgV domain of PD-1 connected to N-terminus of six histidine; present as monomer in solution) using the protocol outlined in Example 1.

[0924] Derivatives of anti-mPD-1 antibody R3A9 (SEQ ID NOs:139-146) by light pair shuffling using the VH chain of R3A9. R3A9 and its derivatives (see, e.g., SEQ ID NOs: 147-167) were select to develop further. The antibodies were cloned and expressed by WuXi Biologics using Wuxi's mammalian expression vector and CHO knockout cell line. The antibodies were purified by protein A and SEC-HPLC. More than 2.5 mg purified antibodies are obtained from 20 ml culture after Protein A purification. Antibodies further purified by SEC-HPLC.

[0925] The biological properties of selected antibodies generated in accordance with the methods of this Example are described in detail in the Examples set forth below. FIGS. **1** and Table 25 provide the amino acid sequences of the heavy and light chain variable regions and CDRs of selected anti-mPD-1 antibodies (Kabat numbering).

Example 19: Anti-mPD-1 Antibody R3A9 and its Derivatives Bind to mPD-1 and Block mPD-1/mPD-L1 Interactions

[0926] Dose Response Binding and Blocking ELISA were performed using R3A9 and its derivatives using the protocols as outlined in Examples 2 and 3. Binding of antibodies to mPD-1 expressing cells was performed as described in Example 4. Blockage of intercellular PD-1/PD-L1 interactions was examined using the Promega Bioassay described in Example 5. The results are illustrated in FIG. **17**.

[0927] The R3A9 derivative m3A7 was found to be more potent than the parental R3A9 antibody in both binding to the soluble cell expressed mPD-1 and blocking mPD-1/mPD-L1 interactions (Table 18).

TABLE 18

Dose response binding of antibodies m3A7 and R3A9 to mPD-1-Fc, streptavidin-captured mPD-1FC, streptavidin-captured mPD-1his, and cells expressing mPD-1; blocking of mPD-1 to PD-L1 by ELISA and blockage of intercellular ineractions between mPD-1 to PD-L1 as determined by a Promega assay. RMP1-14 is a control, monoclonal antibody reacts with mouse PD-1.

EC50/IC50	Description	M3A7 (7115C)	R3A9 (7115A)	RMP1-14
EC 50, nM	mPD-1-Fc	0.834	14.6	
EC 50, nM	Strep captured mPD-1-Fc	0.187	0.156	
EC 50, nM	Strep captured mPD-1-his	0.251	1.61	
EC 50, nM	mPD-1-293	0.228	0.566	
IC 50, nM	Blocking of mPD-1/PD-L1 interaction (ELISA)	0.102	0.441	0.635
IC 50, μg/ml	Blocking of intercellular mPD-1/PD-L1 interaction	0.0709	1.625	5.594

Example 20: R3A9 Derivatives m2C1, m2A1, m4D1 and m3A7 Bind to Both Human and Murine PD-1

[0928] Dose response Binding and Blocking ELISAs for antibodies were performed using the protocols outlined in Examples 2 and 3, respectively. The experiments showed all R3A9 derivatives bound strongly to both hPD-1 and mPD-1 (FIGS. **18**A-C) and blocked hPD-L1-hPD-1 and mPD-L1/mPD-1 interaction (FIG. **18**D-E). Table 19 provides EC50/IC50 data for the antibodies tested.

TABLE 19

Binding of antibodies 38B2, m2C1, m2A1, m4D1, m3A7, and R3A9 to hPD-1, mPD-1, and streptavidin-captured biotin mPD-1, and blocking of mPD-1/mPD-L1 or hPD1/hPDL1 interactions by antibodies 38B2, m2C1, m2A1, m4D1, m3A7, and R3A9.

EC50/ IC50, nM	Target	hPD1 Ab (38B2)	m2C1	m2A1	m4D1	m3A7	mPD1 parental (R3A9)
EC50, nM	hPD1	0.125	0.1494	0.1465	0.2208	0.6302	3.246
EC50, nM	mPD1	No binding	0.5715	0.3039	2.032	0.3495	1.356
EC50, nM	strep capt. Biotin-mPD1	No binding	0.2912	0.1404	1.15	0.2681	0.462
IC50, nM	mPD1/ mPDL1	No binding	0.4641	0.442	0.8818	0.5373	0.722
IC50, nM	hPD1/ hPDL1	4.25	5.707	6.01	6.02	37.77	No binding

Example 21: R3A9 Bind to Cells Expressing Human or Mouse PD-1

[0929] Binding of R3A9 and its R3A9 derivatives m2A1, m2C1, m4D1, m3A7 to PBMCs cells were tested using the protocol outlined in Example 4. Further, Biacore analysis was performed on all the antibodies disclosed in this Example using the protocol provided in Example 11.

[0930] Only three derivatives, m4d1, m2AM, and m3CM, were found to bind to both human and mouse PD-1 expressed on cells (Table 21 and FIG. **19**). Based on cell binding (Table 20) and Biacore analysis (Table 20), m4D1 was found to show improved binding properties as compared to the other two antibodies tested (Table 20 and FIG. **19**).

TABLE 20

Binding affinity data for indicated antibodies as determined by SPR.

	Biacore Analysis								
	mPD1-his			mPD1-Fc			hPD1-Fc		
Name	k_a (1/Ms)	k_d (1/s)	K_D (M)	k_a (1/Ms)	k_d (1/s)	K_D (M)	k_a (1/Ms)	k_d (1/s)	K_D (M)
38B2		no binding			no binding		2.21E+05	3.26E−05	1.47E−10
m2A1	3.75E+05	1.07E−03	2.83E−09	3.33E+05	9.05E−04	2.73E−09	2.40E+05	4.01E−04	1.67E−09
m2C1	2.15E+05	6.93E−04	3.22E−09	2.00E+05	5.83E−04	2.91E−09	1.26E+05	3.55E−04	2.81E−09
m4D1	7.00E+04	2.01E−04	2.87E−09	6.63E+04	1.79E−04	2.69E−09	5.83E+04	6.36E−05	1.09E−09
m3A7	2.72E+05	8.23E−04	3.03E−09	2.61E+05	6.59E−04	2.53E−09	1.71E+05	1.76E−02	1.03E−07
m3A7	2.41E+05	4.79E−04	1.98E−09	2.19E+05	4.06E−04	1.86E−09	1.32E+05	2.63E−03	1.99E−08
R3A9	4.09E+05	6.41E−03	1.57E−08	1.16E+05	1.40E−03	1.21E−08		no binding	

TABLE 21

Binding of antibodies m2A1, m2C1, m4D1, R3A9, m3A7 and 38B2 to cells expressing hPD-1 or mPD-1.

	EC50 of cells expressing h/mPD1, nM			
Name	hPD1-293	hPD1-Jurkat	mPD1-293	mPD1-eff
38B2	0.267	0.137	ND	ND
m2A1	0.987	ND	0.433	0.253

TABLE 21-continued

Binding of antibodies m2A1, m2C1, m4D1, R3A9, m3A7 and 38B2 to cells expressing hPD-1 or mPD-1.

	EC50 of cells expressing h/mPD1, nM			
Name	hPD1-293	hPD1-Jurkat	mPD1-293	mPD1-eff
m2C1	1.263	very weak	0.411	0.373
m4D1	1.48	0.738	1.139	0.441
m3A7	ND	ND	0.609	0.27
m3A7 *	NA	NA	NA	N
R3A9	ND	ND	0.314	0.645

Example 22: Promega (h/m)PD-1/(h/m)PD-L1 Blockade Bioassay Comparing m4D1 with 38B2 and m3A7

[0931] Promega blockade bioassays were performed to compare the potency of m4D1, m3A7 and 38B2 to disrupt intercellular PD-1/PD-L1 interactions using the protocol outlined in Example 4. The results are depicted in FIG. **20**.

[0932] m4D1 was found to block both hPD-1/PD-L1 and mPD-1/mPD-L1 interactions. Further, m4D1 was found to be as potent as m3A7 in mPD-1/mPD-L1 blockade assay and 3 folds less potent than 38B2 (FIG. **20**).

Example 23: Fusion Proteins Comprising Anti-mPD1- or Anti-hPD-1 Antibodies, IL-15 and, IL-15Rα Sushi Domain

[0933] Anti-mPD-1 fusion antibodies comprising antibody m3A7 (referred to as m3A7/IL-15) were engineered by appending the sushi-domain of IL-15Rα and an IL-15 polypeptide to either the C-terminus or N-terminus of the antibody. The fusion of the IL-15Rα sushi domain along with a portion of the hinge region, linker 1, and IL-15 is called "SD15." See, for an example of an SD15 domain, SEQ ID NO:174 in Table 25, SD15 domain highlighted in bold.

[0934] In the first version of the fusion protein, the SD15 domain was fused to the C-terminus of only one of the IgG1 CH1-CH2-CH3 domain (designated "1C-m3A7/IL-15").

[0935] In a second version, the SD15 domain was fused to the C-termini of both IgG1 CH1-CH2-CH3 domains (designated "2C-m3A7/IL-15").

[0936] In a third version of the fusion protein, the SD15 domain was linked to the N-terminus of only one of the VH domains via a second linker (designated "1N-m3A7/IL-15").

[0937] In a fourth version of the fusion protein, the SD15 domain was linked to the N-terminus of both of the VH domains via a second linker (designated "2N-m3A7/IL-15).

[0938] In the four constructs above, the light chains were that of a conventional antibody. Amino acid substitutions, L234A, L235A, P329G (LALA-PG) were introduced in both the CH2 domains for eliminating complement binding and fixation as well as Fc-7 dependent antibody-dependent cell-mediated cytotoxity (ADCC).

[0939] Further, for heterodimeric fusions, mutations were introduced into constant regions of the heavy chains, wherein the amino acid substitutions were selected from one of the following groups: (1) CH3-1:T366Y ("knob"); CH3-2: Y407T ("hole"), (2) CH3-1: S354C, T366W ("knob"); CH3-2: Y349C, T366S, L368A, Y407V ("hole") and (3) CH3-1: T350V, L351Y, F405A, Y407V ("knob"); CH3-2: T350V, T366L, K392L, T394W ("hole").

[0940] The fusion antibodies were expressed transiently in CHOk cells. At least 95% purity of the monomer was obtained after purification with Protein A and SEC-HPLC. Four corresponding versions of anti hPD-1/IL-15 fusion antibodies comprising antibody 38B2 (described herein as 38B2-hSD15 or 38B2/IL-15)—1C-38B2-hSD15, 2C-38B2-hSD15, 1N-38B2-hSD15, 2N_-38B2-hSD15—were created following the same procedure. Three corresponding versions of 1N_38B2-SD15 bearing an amino acid substitution in position 65 of the IL-15 sequence, 65A_1N_38B2-hSD15, 65D_1N_38B2-hSd15, and 65S_1N_38B2-hSD15 were created using the same procedure.

[0941] Four corresponding versions of control fusion antibodies (DP47/IL-15) 1C-DP47/IL-15, 2C-DP47/IL-15, 1N-DP47/IL-15, 2N-DP47/IL-15 were created following the same procedure. DP47 was used as a non-targeting control antibody. Schematic diagram showing the antibody orientations are shown in FIG. **21**.

Example 24: mPD-1/IL-15 Fusion Molecules Bind to Murine PD-1 and Block Interactions Between mPD-1 and mPD-L1

[0942] The ability of fusion proteins 1N-m3A7/IL-15, 1C-m3A7/IL-15, 2N-m3A7/IL-15, and 2C-m3A7/IL-15 to bind to mPD-1 and to block interactions between mPD-1 and mPD-L1 was assessed by ELISA, following the protocols described in Example 2 and 3, respectively.

[0943] No significant differences in binding and blocking capacity were observed among the four different molecules (Table 22 and FIG. **22**).

TABLE 22

Binding to mPD-1 and blocking of mPD-L1 to mPD-1 by fusion proteins 1N_m3A7/IL-15, 2N_m3A7/IlL5, 1C_m3A7/IlL5, and 2C_m3A7/IL-15.

Name	Ka	Kd	KD
Binding to mPD-1-his			
2C-m3A7/IL15	2.00E+05	4.94E−05	2.47E−10
2N-m3A7/IL15	9.21E+04	2.61E−05	2.83E−10
1C-m3A7/IL15	2.32E+05	6.87E−05	2.96E−10
1N-m3A7/IL15	1.52E+05	6.95E−05	4.57E−10
Binding to mPD-1-Fc*			
2N-m3A7/IL15	1.15E+05	1.05E−06	9.09E−12
2C-m3A7/IL15	1.81E+05	1.08E−05	5.93E−11

TABLE 22-continued

Binding to mPD-1 and blocking of mPD-L1 to mPD-1 by fusion proteins 1N_m3A7/IL-15, 2N_m3A7/IlL5, 1C_m3A7/IlL5, and 2C_m3A7/IL-15.

Name	Ka	Kd	KD
1N-m3A7/IL15	1.46E+05	1.28E−05	8.78E−11
1C-m3A7/IL15	2.00E+05	1.86E−05	9.27E−11

*The off rate was too slow and outside the machine limit.

Example 25: Effect of mPD-1/IL-15 Fusion Molecules on IL-2-Dependent Cell Growth Stimulation of Mouse Lymphocytes CTLL2 and C57BL6 Spleen Cells

[0944] CTLL2 Culture and Proliferation Assay: The murine T lymphocyte cell line CTLL2 was cultured in IMDM medium supplemented with 10% heat-inactivated FBS and 10% IL-2 supplement (T cell culture supplement with ConA, Corning). The following fusion proteins were tested in this example: 1N-m3A7/IL-15, 2N-m3A7/IL-15, 1C-m3A7/IL-15 and 2C-m3A7/IL-15. 1N-DP47/IL-15, 2N-DP47/IL-15, 1C-DP47/IL-15, 2C-DP47/IL-15 and m3A7 were used as controls.

[0945] Serial dilutions of antibodies or fusion proteins were added in a 96-well plate, and then cells were seeded at 2.5×10^4 per well in IMDM medium supplemented with 10% heat-inactivated FBS. The cells were incubated at 37° C. for 3-5 days and cell proliferation was detected using CellTiter-Glo® luminescent cell viability assay kit (Promega).

[0946] Mouse Spleen Cell Isolation and Proliferation Assay: C57BL/6 mouse spleens were homogenized in IMDM medium through the 70 μm cell strainer. 1×RBC lysis buffer (eBioscience) was added to spleen cells and left for 3 min with occasional shaking, and then diluted with 5-fold volume of PBS buffer. After washing with PBS buffer, the splenocyte cell suspension was prepared in complete IMDM medium supplemented with 10% heat-inactivated FBS for proliferation assay immediately. The following fusion proteins were tested in this example: 1N-m3A7/IL-15, 2N-m3A7/IL-15, 1C-m3A7/IL-15 and 2C-m3A7/IL-15. 1N-DP47/IL-15, 2N-DP47/IL-15, 1C-DP47/IL-15, and 2C-DP47/IL-15 were used as controls.

[0947] Serial dilutions of the fusion proteins and controls were added in a 96-well plate and then cells were seeded at 1×10^5 per well. The cells were cultured for 5-7 days at 37° C. and collected for flow-cytometry analysis. The cells were washed and stained with fixable viability dye Fluor780 (eBioscience) for 30 min at 4° C. The cells were fixed after washing and were permeabilized with Foxp3 transcription factor staining buffer set (eBioscience), followed by staining with CD3(145-2C11)-PE, CD4(RM4-5)-APC, CD8α-(53-6.7)-PECy7 and Ki67(SolA15)-FITC from eBioscience. Proliferative CD4 ($CD4^+Ki67^+$) or CD8 ($CD8^+Ki67^+$) T cell population were analyzed and defined using Guava Flow Cytometry EasyCyte system.

[0948] All mPD-1/IL-15 fusion constructs stimulated both IL-2 dependent mouse lymphocyte CTLL2 (FIG. **23**A) and C57BL6 spleen cell growth (FIG. **23**B). Analysis of T cell populations showed that only the percentage of $CD8^+$ T cell population increased while the population percentage of $CD4^+$ T cells remained unaffected (FIG. **23**C). Out of the four constructs tested, 1N-m3A7/IL-15 showed the least

stimulatory effect on IL-2 dependent mouse lymphocyte and spleen cell growth and T cell proliferation, while 2C-m3A7/IL-15 showed the most stimulatory effect on the cell growth and T cell proliferation.

Example 26: Efficacy Study of mPD-1/IL-15 Fusion Molecules in PD-1/PD-L1 Lewis Lung Cancer Model

[0949] To determine if the orientation or the number of IL-15/IL-15Rα sushi domains in a fusion protein have any effect on the ability of the fusion molecules to reduce tumor growth, an in vivo efficacy study in an LL/2 Murine Lung Cancer Syngeneic Model was conducted by Crown Bioscience (Taicang) using the m3A7/IL-15/IL-15Rα sushi fusion proteins Inc. Constructs 1N-m3A7/IL-15 and 1C-m3A7/IL-15 were tested in this Example, while 1N-DP47/IL-15 and 1C-DP47/IL-15 were used as controls.

[0950] C57BL6 strain mice, age from 8 to 10 weeks and weight from 16.5 to 20.7 g, were purchased from Shanghai Lingchang Biotechnology Co., Ltd (Shanghai, China). The LL/2 tumor cells were maintained in vitro with DMEM medium supplemented with 10% fetal bovine serum at 37° C. in presence of 5% CO2. The cells were harvested in exponential growth phase and counted before tumor inoculation. The fusion proteins used in this example were produced by WuXi Biologics and exhibited at least 95% purities and contained more than 95% monomer.

[0951] Each mouse was inoculated subcutaneously at the right rear-flank region with LL/2 tumor cells (3×10^5) in 0.1 ml of PBS for tumor development. The date of randomization and the first dosing day was denoted as day 0. When the mean tumor size reached approximately 100 mm^3 the randomization process was started. Mice were randomly allocated to different study groups. Randomization was performed based on a "matched distribution" method using the multi-task method (StudyDirector™ software, version 3.1. 399.19) randomized block design.

[0952] The fusion proteins were diluted according to the indicated dose and 10 μl/kg of fusion proteins was injected intravenously to the mice once every week for three weeks. The mice were weighed twice per week after randomization. Tumor volumes were measured twice per week in two dimensions using a caliper, and the volume was expressed in mm^3 using the formula: "V=(L×W×W)/2, where V denoted tumor volume, L denoted tumor length (the longest tumor dimension) and W denoted tumor width (the longest tumor dimension perpendicular to L). Dosing as well as tumor and body weight measurements were conducted in a Laminar Flow Cabinet. The body weights and tumor volumes were measured by using StudyDirectorm software (version 3.1. 399.19).

[0953] To determine antitumor activity of the fusion proteins, tumor growth inhibition (TGI) percentages were measured and recorded daily using the following formula TGI (%)=100×(1−T/C), where T and C denoted mean tumor volume (or weight) of the treated and control groups respectively for each of the fusion proteins and controls.

[0954] Of the fusion proteins tested, 1N-m3A7/IL-15 showed the most inhibitory effect on tumor growth (Table 23 and FIG. **24**).

[0955] Taken together, the data obtained from Examples 25 and 26 suggests that compared to the C-terminal fusion antibodies, the N-terminal fusion antibodies reduce the toxicity further because of the lower stimulation for the peripheral T cells. The data further shows that the N-terminal fusion molecules are particularly effective in stimulating tumor infiltrating lymphocytes (TIL) as compared on peripheral T cells due to the cis-presentation; the reduction of IL-2Rβγ binding in N-terminal fusion molecules allows the PD-1/IL-15 to selectively bind to TIL, therefore reducing its toxicity. Finally, the data shows that 1N-fusion molecules are superior to the 2N-fusion molecules.

TABLE 23

Ability of anti-PD-L1-SD15 fusion proteins to prolong survival of mice bearing PD-1 expressing tumors in PD-1/PD-L1 resistant Lewis Lung Model. RMP1-14 is a control, monoclonal antibody reacts with mouse PD-1.

	Name					
	Antibody		2 × IL15 fusions		1 × IL15 fusioons	
	RMP1-14	m3A7	2C	2N	1C	1N
Dose mg/kg	10	10	3.3	3.3	5.9	5.9
nmol/kg	66.7	66.7	17.5	17.5	35.0	35.0
Frequency, route	BIW, IP		QW, IP		QW, IP	
Tumor growth inhibition, %	−4.9 ± 36.6	9.6 ± 34.9	56.4 ± 25.2	49.7 ± 21.4	53.1 ± 16.7	75.4 ± 12.5

Example 27: hPD-1/IL-15 Fusion Proteins Retained their PD-1/PD-L1 Inhibitory Function

[0956] Promega Blockade Bioassay was performed as described in Example 5 using fusion proteins 1C-38B2-hSD15, 2C-38B2-hSD15, 1N-38B2-hSD15, 2N-38B2-hSD15, 1N-65D-hSD15-38B2, and 1N-65S-hSD15-38B2. All fusion molecules retained PD-1/PD-L1 inhibitory functions as compared to 38B2 (FIG. **26**). 1N-fusions provided the most PD-1/PD-L1 inhibitory functions.

Example 28: hPD-1/IL-15 Fusion Proteins Stimulate IL-15 Activity

[0957] ExaM07e Culture and Proliferation Assay: To determine the ability of the fusion proteins to stimulate IL-15 in vitro, the human acute megakaryoblastic leukemia M07e cell line was cultured in INDM medium supplemented with 15% heat-inactivated FBS and 20% conditioned medium of cell line 5637.

[0958] Serial dilutions of antibodies or fusion proteins were added to a 96-well plate, and then cells were seeded at 2.5×10^4 per well in INDM medium supplemented with 10% heat-inactivated FBS. The cells were incubated at 37° C. for 3-5 days and cell proliferation was detected using CellTiter-Glo® luminescent cell viability assay kit (Promega).

[0959] While all tested fusion protein constructs stimulated IL-15 activity, IN fusions showed a decreased ability to stimulate as compared to 1C, 2C, or 2N constructs (FIG. **27**).

Example 29: Efficacy Study of hPD-L1/SD15 Fusion Molecules in CT26 Syngeneic Models

[0960] To determine if the orientation or the number of IL-15/IL-15Rα sushi domains have any effect on the ability of the fusion molecules to inhibit tumor growth, an in vivo efficacy study was performed in a CT26 syngeneic model

using 1N-SD15-D7A8, 2N-SD15-D7A8, 1C-SD15-D7A8, and 2C-SD15-D7A8. CT26 syngeneic model mice were treated with the fusion proteins and observed for tumor development/reduction. CT26 is a murine colon carcinoma line.

[0961] Tumor volumes were measured twice per week in two dimensions using a caliper, and the volume was expressed in mm^3 using the formula: "V=(L×W×W)/2, where V denoted tumor volume, L denoted tumor length (the longest tumor dimension) and W denoted tumor width (the longest tumor dimension perpendicular to L). Dosing as well as tumor and body weight measurements were conducted in a Laminar Flow Cabinet. The body weights and tumor volumes were measured by using StudyDirectorm software (version 3.1.399.19).

[0962] Results of the efficacy study with PD-L1/IL-15 molecules are shown in FIG. **28**.

Example 30: The Presence of IL-5 Amino Acid Substitutions in the 1N-Fusion Proteins Did not Affect the Fusion Protein's PD-1/PD-L1 Inhibitory Function

[0963] Promega Blockade Bioassays (FIG. **26**C, FIG. **29**E, and FIG. **29**F) and ELISA competition assays (FIGS. **29**B and **29**C) showed that N65S or N65D amino acid substitutions in 1N-fusion proteins comprising IL-15 did not affect the ability of the fusion proteins to effectively disrupt PD-1/PD-L1 or PD-1/PD-L2 interactions.

[0964] Similarly, no significant differences were observed in the strong binding of 1N-fusion proteins comprising wild-type IL-15 or IL-15 N65S, respectively, to soluble PD-1 or cells expressing PD-1 (FIGS. **29**A and **29**D).

Example 31: 1N-Fusion Proteins Comprising an IL-15 Amino Acid Substitution Showed Weaker IL-15 Simulation In Vitro

[0965] The ability of 1N-fusion proteins to stimulate IL-15 activity in human and in mouse cells was examined. In the presence of N65S-1N-IL-15/38B2, human acute megakaryoblastic leukemia cells (M07e, FIGS. **30**A, **30**B, and **30**C), hPBMCs (FIG. **30**D), IL-2/IL-15-dependent murine lymphocyte cell lines (CTLL2, FIG. **31**A), murine spleen cells (FIG. **31**B) grew slower than in the presence of wild type 1N-IL-15/38B2. Binding of N65S-1N-/38B2 to hIL-2Rβ transfected HEK293 diminished (FIG. **30**E).

[0966] Further, both 1N-IL-15/38B2 and mut-1N-IL-15/38B2 induced a better dose response in proliferating $CD8^+$ T cells than $CD4^+$ T cells in both mouse spleen (FIG. **31**C) and hPBMCs (FIG. **31**D).

Example 32: 1N-Fusion Proteins Comprising an IL-15 Amino Acid Substitution Exhibited Strong Anti-Tumor Activity In Vivo in an Anti-PD-1 Antibody-Resistant Mouse Model

[0967] In vivo efficacy of 1N-fusion proteins comprising wild-type IL-15, IL-15 N65S, or IL-15 N65D, respectively, was evaluated in hPD-1/hPD-L1 transgenic BALB/c mice bearing Keytruda (an anti-PD-1 antibody) resistant hPD-L1-CT26 tumors. The fusion antibodies (once per week) and controls (twice per week) were injected (intraperitoneal) when the tumor size reached approximately 100 mms.

[0968] Both 1N-38B2/IL-15 and N65S-1N-38B2/IL-15 exhibited strong antitumor activity (FIG. **32**A). Anti-tumor efficacy of N65S-1N-38B2/IL-15 was dose dependent (FIG. **32**B). 12 mg/kg, QW×3 weeks of N65S-1N-38B2/IL-15 demonstrated tumor regression (FIGS. **32**B and **32**C). No weight loss or mortality was observed with N65S-IN-38B2/IL-15 when dosed at 12 mg/kg, but significant weight loss and mortality were observed with 1N-38B2/IL-15 when dosed at >1 mg/kg (FIG. **32**E and FIG. **32**E). A non-targeting 1N-IL-15 fusion did not show any anti-tumor efficacy. Significant weight loss (FIG. **32**D) and mortality were observed when dosed >1 mg/kg for the non-targeting 1N-IL-15 fusion (data not shown).

[0969] 1N-fusion proteins comprising IL-15 N65S showed improved efficacy as compared to 1N-fusion proteins comprising IL-15 N65D (FIGS. **321** and **32**K).

[0970] In sum, fusion proteins comprising mutated IL-15 lowered IL-15-associated potency and stimulation, resulting in lower toxicity and an increased therapeutic treatment window.

Example 33: 1N-Fusion Proteins Comprising an IL-15 Amino Acid Substitution Exhibited Strong Anti-Tumor Activity In Vivo in Mice that were Rechangelled with Tumor Cells

[0971] In vivo efficacy of 1N-fusion proteins comprising IL-15 N65S or IL-15 N65D, respectively, was evaluated in hPD-1/hPD-L1 transgenic mice.

[0972] 0.5×10^6 of hPDL1/CT26 was subcutaneously inoculated to the right lower flank of the mice. When the tumor size reached to about 100 mm^3, the mice were intraperitoneally injected with 12 mg/kg of N65S-1N-38B2/IL-15 or N65D-1N-38B2/IL-15 once every week and twice every week for three weeks respectively. The tumors in 5 mice (of 6) completely disappeared in about 25 days for N65S-1N-38B2/IL-15 treatment and 40 days for N65D-1N-38B2/IL-15 treatment.

[0973] At day 88, 0.5×10^6 of hPDL1/CT26 cells and 0.1×10^6 of CT26 cells were subcutaneously inoculated to the left lower flank and left upper flank respectively. No tumor growth was observed for both cell lines up to day 135 days, showing that the fusion protein protect mice against rechallenges with tumor cells (FIG. **33**).

Example 34: 1N-Fusion Proteins Comprising an IL-15 Amino Acid Substitution Exhibited Improved Anti-Tumor Activity in hPD1/PDL1 Mice Bearing hPDL1-CT26 Tumor as Compared to Combinations of Non-Targeted Fusion Protein and an Anti-PD-1 Antibody

[0974] 0.5×10^6 of hPDL1/CT26 cells were subcutaneously inoculated to the right lower flank of the mice. When the tumor size reached to about 100 mm^3, the mice were intraperitoneally injected with 10 mg/kg of 38B2, 12 mg/kg of N65S-1N-38B2/IL-15, and combination of 10 mg/kg of 38B2 with 12 mg/kg of N65S-1N-DP47/IL-15 once every week for three weeks respectively. For the combination treatment, two test articles were injected sequentially with one hour.

[0975] The ability to suppress tumor growth was compared for the following constructs: (1) N65S-1N-38B2/IL-15 fusion protein; (2) a non-targeted fusion N65S-1N-DP47/IL-15; (3) a combination of anti-PD-1 antibody 38B2 and the non-targeted fusion (i.e., N65S-1N-DP47/IL-15); and (4) anti-PD-1 antibody 38B2 only.

[0976] Tumors grew significantly slower in the N65S-1N-38B2/IL-15 group as compared to the combination group (FIG. **34**A). 83% (5/6) of the mice were tumor-free in the N65S-1N-38B2/IL-15 fusion group, while no tumor-free mice were observed in the combination group and one tumor-free mouse was observed in the anti-PD-1 antibody 38B2 only group. (FIG. **34**B). No body weight loss was observed for 65S-1N-IL15/38B2 fusion group, about −5% bodyweight loss for non-targeted fusion 65S-1N-IL15/DP47 group (FIG. **34**C).

[0977] This data illustrates the robust anti-tumor activity of N65S-1N-38B2/IL-15 fusion proteins and highlights its bi-functionality and its ability to bind to both PD1 and IL2Rβγ, which are co-expressed on TILs.

Example 35: Additional Administration of an Anti-PD-1 Antibody does not Lead to a Further Increase in Anti-Tumor Activity of 1N-Fusion Proteins

[0978] 0.5×10^6 of hPDL1/CT26 cells were subcutaneously inoculated to the right lower flank of the mice. When the tumor size reached to about 100 mm^3, the mice were intraperitoneally injected with 10 mg/kg of 38B2, 12 mg/kg of N65S-1N-38B2/IL-15, and combination of 10 mg/kg of 38B2 with 12 mg/kg of N65S-1N-38B2/IL-15 once every week for three weeks respectively. For the combination treatment, two test articles were mixed first, then injected to the mice.

[0979] The ability to suppress tumor growth was compared for the following constructs: (1) N65S-1N-38B2/IL-15 fusion protein; (2) a combination of anti-PD-1 antibody 38B2 and N65S-1N-38B2/IL-15 fusion protein; and (3) anti-PD-1 antibody 38B2 only.

[0980] Tumor grew significantly more slowly in the N65S-1N-38B2/IL-15 group as compared to the combination group (FIG. **35**A). 83% (5/6) mice were tumor-free in the N65S-1N-38B2/IL-15 group, no tumor-free mice were observed in the combination group and one tumor-free mouse was observed in the antibody only (FIG. **35**B). The bodyweight is shown in FIG. **35**C.

[0981] This data shows that 1N-fusion proteins are more effective in reducing tumor growth than combinations of 1N-fusion proteins and anti-PD-1 antibodies.

Example 36: N65S-1N-38B2/IL-15 Fusion Protein Showed a Long Serum Half-Life in hPD1/PDL1 Transgenic Mice Bearing hPDL1-CT 26 Tumors

[0982] hPD1/PDL1 transgenic Balb/c mice were inoculated subcutaneously at the right lower flank with hPDL1/CT26 tumor cells (0.5×10^6) in 0.1 mL of PBS. The animals were randomized and treatments were started when the average tumor volume reaches approximately 83 mms. The 5.1 mg/kg (0.35 μmol/kg) of 38B2, or 1 or 6 mg/kg (0.06 or 35 μmol/kg) of N65S-1N-38B2/IL-15 were administrated to the mice either intraperitoneally (IP) or intravenously (IV). After dosing, blood was collected at 0.2 h, 5 h, 2 h, 4 h, 12 h, 24 h, 48 h, 72 h, 120 h and 168 h post injection and the purified serum were used to measure the antibody concentration by the traditional ELISA, in which human PD1 was used as the captured protein and biotin-IL15 and anti-human Fab was used separately to detect the KD050 and 38B2 binding.

[0983] N65S-1N-38B2/IL-15 exhibited a similar serum half-life profile as antibody 38B2 in both IV (FIG. **36**A) and IP (FIG. **36**B) injection with dose response up to 120 h after treatment.

Example 37: Mechanism of Action Study in hPDL1/PD1 Transgenic BALB/c Mice Bearing hPDL1-CT26 Tumors

[0984] 0.5×10^6 of hPDL1/CT26 cells were subcutaneously inoculated to the right lower flank of the hPD1/PDL1 transgenic BALB/c mice. When the tumor size reached to about 17 5 mms, the mice were intravenously injected with 0.06 or 0.35 μmol/kg each of (1) N65S-1N-38B2/IL-1, (2) N65S-1N-DP47/IL-15 (non-targeted control), (3) antibody 38B2 and (4) the combination of antibody 38B2 and N65S-1N-38B2/IL-15. The tumor size was measured twice per week and mice were terminated at day 7 after dosing (FIG. **37**A). Blood and draining lymph node (DLN) from all groups were collected to perform flow cytometry. Tumors were collected to perform TILs analysis (FIG. **37**B). One-way ANOVA was used for statistical analysis. When a significant F-statistics (a ratio of treatment variance to the error variance) was obtained, comparisons between different groups were carried out with Games-Howell (equal variances not assumed) or Tukey (equal variances assumed) test. Comparisons between vehicle and other groups, * $p<0.05$; ** $p<0.01$; *** $p<0.001$. Error bars represented Standard Error of Mean (SEM).

[0985] It was shown that N65S-1N-38B2/IL-15 bound to PD1 and IL2Rβγ expressing TIL and differently proliferated CD8+ T cells. Specifically, when analyzing the CD8/CD4 ratio in tumors, the blood, and draining lymph nodes (treated with antibody (1) 38B2, (2) PD1 targeted fusion protein N65S-1N-38B2/IL-15, (3) non-targeted fusion protein N65S-1N-DP47/IL-15, or (4) a combination of 38B2 and N65S-1N-38B2/IL-15), it was found that N65S-1N-38B2/IL-15 promoted $CD8^+$ T cells growth in tumor, but not in the blood and draining lymph nodes. The CD8/CD4 ratio did not change as result of the other treatments ( )1) 38B2, (2) non-targeted fusion protein N65S-1N-DP47/IL-15, or (3) a combination of 38B2 and N65S-1N-38B2/IL-15)) (FIG. **37**C).

[0986] Next, CD8 and CD4 subtypes in tumors (treated with antibody (1) 38B2, (2) PD1 targeted fusion protein N65S-1N-38B2/IL-15, (3) non-targeted fusion protein N65S-1N-DP47/IL-15, or (4) a combination of 38B2 and N65S-1N-38B2/IL-15) were analyzed. It was found that effector memory CD8 T cells were significantly increased in the tumor for N65S-1N-38B2/IL-15 reated samples and slightly increased for the 38B2 treated samples (FIG. **37**D). No difference was observed among the other T cell subtypes in different treatment groups.

Example 38: N65S-1N-m3A7/IL-15 (Surrogate) Efficacy Studies in Multiple Mouse Syngeneic Tumor Models

[0987] The indicated amount of tumor cells (Table 24) in 0.1 mL of PBS was subcutaneously inoculated to the right flank of the mice. The animals were randomized and treatments were started when the average tumor volume reaches approximately 100 mms (between 75-125 mm^3). Tumor volumes were measured 2 times per week in two dimensions using a caliper, and the volume was expressed in mm^3 using the formula: $V=(L\times W\times W)/2$, where V is tumor volume, L is tumor length (the longest tumor dimension) and W is tumor width (the longest tumor dimension perpendicular to L).

[0988] Significant anti-tumor efficacies were observed in all 12 models (TGI>50%) in single dose treatment (Table 24). Completed response (tumor free) were found for CT26, EMT6, MC38, H22, A20 and Pan02 (Table 24). Data for EMT6 as shown as an illustrative example (FIG. **38**).

TABLE 24

Results of N65S-IN-m3A7/IL-15 (surrogate) efficacy studies in multiple mouse syngeneic tumor models.

Model	Number of cells	Cancer type	Mouse strain (sex)	Dose, route	TGI (%) (day)	CR (%)	p
CT26	5×10^5	colorectal	BALB/C (F)*	12 mg/kg, IP	93.0 (d17)	75.0	<0.0001
EMT6	5×10^5	breast	BALB/C (F)	12 mg/kg, IP	79.7 (d21)	71.4	<0.0001
Renca	1×10^6	kidney	BALB/C (F)	6 mg/kg, IP	52.4 (d18)	—	<0.0001
MC38	1×10^6	colorectal	C57BL/6 (F)	6 mg/kg, IP	73.7 (d18)	12.5	<0.0001
Hepa1-6	5×10^6	liver	C57BL/6 (F)	6 mg/kg, IV	76.4 (d23)	—	<0.0001
H22	1×10^6		BALB/C (F)	6 mg/kg, IV	89.8 (d18)	30.0	<0.0001
LL2	3×10^5	lung	C57BL/6 (F)	6 mg/kg, IP	68.3 (d15)	—	<0.0001
A20	5×10^5	lymphoma	BALB/C (F)	6 mg/kg, IP	76.5 (d15)	40.0	<0.0001
B16-BL6	2×10^5	melanoma	C57BL/6 (F)	6 mg/kg, IV	46.7 (d13)	—	0.0033
B16-F10	2×10^5		C57BL/6 (F)	6 mg/kg, IV	60.2 (d9)	—	0.0003
Pan02	3×10^6	pancreatic	C57BL/6 (F)	6 mg/kg, IV	76.3 (d30)	30.0	0.0380
RM-1	1×10^6	prostate	C57BL/6 (M)	6 mg/kg, IV	73.0 (d10)	—	<0.0001

F = female.

M = male.

TGI = tumor growth inhibition.

CR = completed response.

TABLE 25

Sequences of the disclosure

Identifier	Sequence	SEQ ID NO
	Antibodies isolated from phage display library	
19B6 HCDR1	GYTFTGYYMH	1
19B6 HCDR2	IINPSGGSTSYAQKFQG	2
19B6 HCDR3	TAGYDWLPSGLGMDV	3
19B6 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQ APGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVY MELSSLRSEDTAVYYCAKTAGYDWLPSGLGMDVWGQGTT VTVSS	4
19B10 HCDR1	GFTFSSYAMH	5
19B10 HCDR2	GISNSGGNTYYADSVKG	6
19B10 HCDR3	DNYYYYMDV	7
19B10 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMHWVRQA PGKGLEWVSGISNSGGNTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCARDNYYYYMDVWGKGTTVTVSS	8
23A8 HCDR1	GFTFSSSAMH	9
23A8 HCDR2	GISGSGSSTYYADSVKG	10
23A8 HCDR3	DNNYYYYMDV	11
23 A8 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSSAMHWVRQAP GKGLEWVSGISGSGSSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARDNNYYYYMDVWGKGTTVTVSS	12
23A11 HCDR1	GYTFTDYSLH	13
23A11 HCDR2	EVIPMEDTAYYAQTFQG	14
23 A11 HCDR3	EPFTMVRGGRYYYYGMDV	15
23A11 VH	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYSLHWVRQA PGQGLEWMGEVIPMFDTAYYAQTFQGRVTITADESTSTAY MELSSLRSEDTAVYYCAREPFTMVRGGRYYYYGMDVWGQ GTTVTVSS	16
23H9 HCDR1	GGTFSSSVIS	17
23H9 HCDR2	GIIPIFGTANYAQKFQG	18
23H9 HCDR3	EGLGCSGGSCYSGYYYGMDV	19
23H9 VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSSVISWVRQAP GQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYME LSSLRSEDTAVYYCAREGLGCSGGSCYSGYYYGMDVWGQ GTTVTVSS	20
24H9 HCDR1	GFTFSSYWMS	21
24H9 HCDR2	AISGSGGSTYYADSVKG	22
24H9 HCDR3	SPLQWVDV	23
24H9 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQA PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCASSPLQWVDVWGQGTTVTVSS	24

TABLE 25-continued

Sequences of the disclosure

Identifier	Sequence	SEQ ID NO
19B6 LCDR1	RASQSINSWLA	25
19B6 LCDR2	YASSLQS	26
19B6 LCDR3	QQGYSVPLS	27
19B6 VL	DIQMTQSPSSLSASVGDRVTITCRASQSINSWLAWYQQKPG KAPKLLIYYASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQGYSVPLSFGQGTKLEIK	28
19B10 LCDR1	RASQSVSTWLA	29
19B10 LCDR2	AASNLET	30
19B10 LCDR3	QQTYSTPYT	31
19B10 VL	DIQMTQSPSSLSASVGDRVTITCRASQSVSTWLAWYQQKPG KAPKLLIYAASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQTYSTPYTFGQGTKLEIK	32
23A8 LCDR1	RASQSIGTWLA	33
23A8 LCDR2	AASTLRS	34
23A8 LCDR3	QQSYSTPYT	35
23 A8 VL	DIQMTQSPSSLSASVGDRVTITCRASQSIGTWLAWYQQKPG KAPKLLIYAASTLRSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPYTFGQGTKLEIK	36
23A11 LCDR1	RASQNINKNLN	37
23 A11 LCDR2	DASNLQS	38
23A11 LCDR3	QHSET	39
23A11 VL	DIQMTQSPSSLSASVGDRVTITCRASQNINKNLNWYQQKPG KAPKLLIYDASNLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQHSETFGQGTKVEIK	40
23H9 LCDR1	RSSQSLLHSNGYNYLD	41
23H9 LCDR2	LSSHRAS	42
23H9 LCDR3	MQGAHWPYT	43
23H9 VL	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYL QKPGQSPQLLIYLSSHRASGVPDRFSGSGSGTDFTLKISRVEA EDVGVYYCMQGAHWPYTFGQGTKVEIK	44
24H9 LCDR1	RASQGISSWLA	45
24H9 LCDR2	SASSLQS	46
24H9 LCDR3	QQANSFPFT	47
24H9 VL	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPG KAPKLLIYSASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQANSFPFTFGPGTKVDIK	48

23H9 derivatives obtained by light pair shuffling using the VH chain of 23H9

31B1 LCDR1	RSSQSLLHSNGYNYLD	41
31B1 LCDR2	EASSLHS	49
31B1 LCDR3	MQGTHWPYT	50
31B1 VL	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYL QKPGQSPQLLIYEASSLHSGVPDRFSGSGSGTDFTLKISRVEA EDVGVYYCMQGTHWPYTFGQGTKVEIK	51
33C4 LCDR1	RSSQSLLHSNGYNYLD	41
33C4 LCDR2	EASSLHT	52
33C4 LCDR3	MQGSHWPYT	53
33C4 VL	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYL QKPGQSPQLLIYEASSLHTGVPDRFSGSGSGTDFTLKISRVEA EDVGVYYCMQGSHWPYTFGQGTKLEIK	54
33G8 LCDR1	RSSQSLLHSNGYNYLD	41
33G8 LCDR2	QASTLGS	55
33G8 LCDR3	MQGTHWPYT	56
33G8 VL	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYL QKPGQSPQLLIYQASTLGSGVPDRFSGSGSGTDFTLKISRVE AEDVGVYYCMQGTHWPYTFGQGTKLEIK	57
34C1 LCDR1	RSSESLLYSNGNTYLD	58
34C1 LCDR2	EVSNRAS	59
34C1 LCDR3	MQGTRWPYT	60
34C1 VL	DIVMTQSPLSLPVTPGEPASISCRSSESLLYSNGNTYLDWYL QKPGQSPQLLIYEVSNRASGVPDRFSGSGSGTDFTLKISRVE AEDVGVYYCMQGTRWPYTFGQGTKVEIK	61
23H9 derivatives motif LCDR1	$RSSX_1SLLX_2SNGX_3X_4YLD$ wherein X_1 is Q or E; wherein X_2 is H or Y; wherein X_3 is Y or N; and wherein X_4 is T or N	62

TABLE 25-continued

Sequences of the disclosure

Identifier	Sequence	SEQ ID NO
23H9 derivatives motif LCDR2	$X_5X_6SX_7X_8X_9X_{10}$ wherein X_5 is L, Q or E; wherein X_6 is S, A, or V; wherein X_7 is H, N, T, or S; wherein X_8 is R or L; wherein X_9 is G, A, or H; and wherein X_{10} is S or T	63
23H9 derivatives motif LCDR3	$MQGX_{11}X_{12}WPYT$ wherein X_{11} is A, T, or S; and wherein X_{12} is H or R	64
23H9 derivatives motif VL	$DIVMTQSPLSLPVTPGEPASISC\ RSSX_1SLLX_2SNGX_3X_4YLD$ WYLQKPGQSPQLLIY $X_5X_6SX_7X_8X_9X_{10}GVPDRFSGSGSGTDFTLKISRVEAEDVGVY$ $YC\ MQGX_{11}X_{12}WPYTFGQGTKVEIK$	65
24H9 derivatives obtained by light pair shuffling using the VH chain of 24H9		
32A11 LCDR1	RASESISIWLA	66
32A11 LCDR2	DASNLET	67
32A11 LCDR3	QQADSFPFT	68
32A11 VL	DIQMTQSPSSLSASVGDRVTITCRASESISIWLAWYQQKPGK APKLLIYDASNLETGVPSRFSGSGSGTNFTLTISSLQPEDFAT YYCQQADSFPFTFGPGTKVDIK	69
32D11 LCDR1	RASQSINIWLA	70
32D11 LCDR2	DASNLET	67
32D11 LCDR3	QQGYSFPFT	71
32D11 VL	DIQMTQSPSSLSASVGDRVTITCRASQSINIWLAWYQQKPGK APKLLIYDASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQGYSFPFTFGPGTKVDIK	72
32D2 LCDR1	RASQGISRWLA	73
32D2 LCDR2	EASTLQS	74
32D2 LCDR3	QQAYSFPFT	75
32D2 VL	DIQMTQSPSSLSASVGDRVTITCRASQGISRWLAWYQQKPG KAPKLLIYEASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQAYSFPFTFGQGTKVDIK	76
32G6 LCDR1	RASQSISSWLA	77
32G6 LCDR2	DASTLQS	78
32G6 LCDR3	QQANSFPFT	47
32G6 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPG KAPKLLIYDASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQANSFPFTFGPGTKVDIK	79
38A10 LCDR1	RASQSISTWLA	80
38A10 LCDR2	DASRLQN	81
38A10 LCDR3	QQGDSFPFT	82
38A10 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISTWLAWYQQKPG KAPKLLIYDASRLQNGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQGDSFPFTFGPGTKVDIK	83
38A11 LCDR1	RASQSISSWLA	77
38A11 LCDR2	DASTLQS	78
38A11 LCDR3	QQGNSFPFT	84
38A11 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPG KAPKLLIYDASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQGNSFPFTFGPGTKVDIK	85
38A4 LCDR1	RASQSISSWLA	77
38A4 LCDR2	DASNLQT	86
38A4 LCDR3	QQANSFPFT	47
38A4 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPG KAPKLLIYDASNLQTGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQANSFPFTFGQGTRLEIK	87
38A6 LCDR1	RASQDISRWLG	88
38A6 LCDR2	AASTLQS	89
38A6 LCDR3	QQANSFPFT	47
38A6 VL	DIQMTQSPSSLSASVGDRVTITCRASQDISRWLGWYQQKPG KAPKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQANSFPFTFGPGTKLEIK	90
38A8 LCDR1	RASESISIWLA	66
38A8 LCDR2	DASNLET	67
38A8 LCDR3	QQANSFPFT	47
38A8 VL	DIQMTQSPSSLSASVGDRVTITCRASESISIWLAWYQQKPGK APKLLIYDASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQANSFPFTFGPGTKVDIK	91

TABLE 25-continued

Sequences of the disclosure

Identifier	Sequence	SEQ ID NO
38B1 LCDR1	RASQSISTWLA	80
38B1 LCDR2	EASKLER	92
38B1 LCDR3	QQAYSFPFT	75
38B1 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISTWLAWYQQKPG KAPKLLIYEASKLERGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQAYSFPFTFGPGTKVDIK	93
38B10 LCDR1	RASQSISTWLA	80
38B10 LCDR2	DASTLQT	94
38B10 LCDR3	QQGYSFPFT	71
38B10 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISTWLAWYQQKPG KAPKLLISDASTLQTGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQGYSFPFTFGPGTKVDIK	95
38B2 LCDR1	RASESISSWLA	96
38B2 LCDR2	DASSLES	97
38B2 LCDR3	QQGDSFPFT	82
38B2 VL	DIQMTQSPSSLSASVGDRVTITCRASESISSWLAWYQQKPGK APKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQGDSFPFTFGQGTKLEIK	98
38C11 LCDR1	RASQSISRWLA	99
38C11 LCDR2	DASTVQS	100
38C11 LCDR3	QQANSFPFT	47
38C11 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISRWLAWYQQKPG KAPKLLISDASTVQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQANSFPFTFGPGTKVDIK	101
38C6 LCDR1	RAGRDINKWVA	102
38C6 LCDR2	DASSLQS	103
38C6 LCDR3	QQANSFPFA	104
38C6 VL	DIQMTQSPSSLSASVGDRVTITCRAGRDINKWVAWYQQKPG KAPKLLIYDASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQANSFPFAFGQGTKVEIK	105
38G11 LCDR1	RASENISRWLA	106
38G11 LCDR2	DASSLQS	103
38G11 LCDR3	QQANSFPFT	47
38G11 VL	DIQMTQSPSSLSASVGDRVTITCRASENISRWLAWYQQKPG KAPKLLIYDASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQANSFPFTFGPGTKVDIK	107
38G9 LCDR1	RVSQSISNWLA	108
38G9 LCDR2	DASSLQS	103
38G9 LCDR3	QQANSFPFT	47
38G9 VL	DIQMTQSPSSLSASVGDRVTITCRVSQSISNWLAWYQQKPG KAPKLLIYDASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQANSFPFT	109
38H3 LCDR1	RASQGISTWLA	110
38H3 LCDR2	EASRLQS	111
38H3 LCDR3	QQAYSFPFT	75
38H3 VL	DIQMTQSPSSLSASVGDRVTITCRASQGISTWLAWYQQKPG KAPKLLIYEASRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQAYSFPFTFGPGTKVDIK	112
39A3 LCDR1	RASQSISSWLA	77
39A3 LCDR2	DASSLQS	103
39A3 LCDR3	QQGDSFPLT	113
39A3 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPG KAPKLLIYDASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQGDSFPLTFGQGTKVEIK	114
39B11 LCDR1	RASQSISSWLA	77
39B11 LCDR2	EASRLQS	111
39B11 LCDR3	QQANSFPFT	47
39B11 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPG KAPKLLIYEASRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQANSFPFTFGPGTKVDIK	115
39B3 LCDR1	RASQSIGPWLA	116
39B3 LCDR2	DASNLET	67
39B3 LCDR3	QQANSFPFT	47
39B3 VL	DIQMTQSPSSLSASVGDRVTITCRASQSIGPWLAWYQQKPG KAPKLLIYDASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQANSFPFTFGPGTKVDIK	117
39B6 LCDR1	RASEDISHWLA	118
39B6 LCDR2	DAKDLHP	119
39B6 LCDR3	QQANSFPFT	47
39B6 VL	DIQMTQSPSSLSASVGDRVTITCRASEDISHWLAWYQQKPG KAPKLLIYDAKDLHPGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQANSFPFTFGQGTRLEIK	120

TABLE 25-continued

Sequences of the disclosure

Identifier	Sequence	SEQ ID NO
39F11 LCDR1	RASQSISTWLA	80
39F11 LCDR2	DASTLQS	78
39F11 LCDR3	QQANSFPFT	47
39F11 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISTWLAWYQQKPG KAPKLLIYDASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQANSFPFTFGPGTKVDIK	121
39G5 LCDR1	RASQNINVWLA	122
39G5 LCDR2	DASSLQS	103
39G5 LCDR3	QQANSFPFT	47
39G5 VL	DIQMTQSPSSLSASVGDRVTITCRASQNINVWLAWYQQKPG KAPKLLIYDASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQANSFPFTFGPGTKVDIK	123
39G8 LCDR1	RASQGISPWLA	124
39G8 LCDR2	DASKLET	125
39G8 LCDR3	QQAYSFPFT	75
39G8 VL	DIQMTQSPSSLSASVGDRVTITCRASQGISPWLAWYQQKPG KAPKLLIYDASKLETGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQAYSFPFTFGGGTKVEIK	126
39H11 LCDR1	RASQSIGIWVA	127
39H11 LCDR2	DASNLQS	38
39H11 LCDR3	QQADSFPFT	68
39H11 VL	DIQMTQSPSSLSASVGDRVTITCRASQSIGIWVAWYQQKPG KAPKLLIYDASNLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQADSFPFTFGQGTKVEIK	128
39H2 LCDR1	RASQNIGPWLA	129
39H2 LCDR2	DASTLHS	130
39H2 LCDR3	QQANSFPFT	47
39H2 VL	DIQMTQSPSSLSASVGDRVTITCRASQNIGPWLAWYQQKPG KAPKLLIYDASTLHSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQANSFPFTFGQGTRLEIK	131
39H7 LCDR1	RASQSISNWLA	132
39H7 LCDR2	DASNLQA	133
39H7 LCDR3	QQAYSFPFT	75
39H7 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISNWLAWYQQKPG KAPKLLIYDASNLQAGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQAYSFPFTFGPGTKVDIK	134
24H9 derivatives motif LCR1	$RX_{13}X_{14}X_{15}X_{16}IX_{17}X_{18}WX_{19}X_{20}$ wherein X_{13} is A or V; wherein X_{14} is S or G; wherein X_{15} is Q, E, or R; wherein X_{16} is G, S, D or N; wherein X_{17} is G, S, or N; wherein X_{18} is S, I, R, T, K, P, N,H, or V; wherein X_{19} is L or V; and wherein X_{20} is G or A	135
24H9 derivatives motif LCR2	$X_{21}AX_{22}X_{23}X_{24}X_{25}X_{26}$ wherein X_{21} is S, D, E, or A; wherein X_{22} is S, or K; wherein X_{23} is S, N, T, R, or D; wherein X_{24} is L or V; wherein X_{25} is Q, E, or H; and wherein X_{26} is S, N, A, R, P, or T	136
24H9 derivatives motif LCR3	$QQX_{27}X_{28}SFPX_{29}X_{30}$ wherein X_{27} is A, or G; wherein X_{28} is N, D, or Y; wherein X_{29} is F or L; and wherein X_{30} is A, or T	137
24H9 derivatives motif VK (see SEQ ID NOS: 135-137 for X_n)	$DIQMTQSPSSLSASVGDRVTITCRX_{13}X_{14}X_{15}X_{16}IX_{17}X_{18}WX_{19}X_{20}$ $WYQQKPGKAPKLLIYX_{21}AX_{22}X_{23}X_{24}X_{25}X_{26}GVPSRFSGSGSG$ $TDFTLTISSLQPEDFATYYCQQX_{27}X_{28}SFPX_{29}X_{30}FGPGTKVDI$ K	138

Mouse/human PD-1 crossreactive antibodiy isolated from phage display

R3A9 HCDR1	GHTFTSYYIH	139
R3A9 HCDR2	GIINPSGGSTSYAQKFQG	140
R3A9 HCDR3	DRAYGGAGDY	141
R3A9 VH	QVQLVQSGAEVKKPGASVKVSCKASGHTFTSYYIHWVRQA PGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCARDRAYGGAGDYWGQGTLVTVSS	142

TABLE 25-continued

Sequences of the disclosure

Identifier	Sequence	SEQ ID NO
R3A9 LCDR1	RASQSVGTWLA	143
R3A9 LCDR2	SASTLQS	144
R3A9 LCDR3	QQSYSAPLT	145
R3A9 VL	DIQMTQSPSSLSASVGDRVTITCRASQSVGTWLAWYQQKPG KAPKLLIYSASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSAPLTFGGGTKVEIK	146
R3A9 derivatives obtained by light pair shuffling using the VH chain of R3A9		
m3A7 LCDR1	RASRSISNWLA	147
m3A7 LCDR2	AASSLQS	148
m3A7 LCDR3	QQSYSAPVT	149
m3A7 VL	DIQMTQSPSSLSASVGDRVTITCRASRSISNWLAWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSAPVTFGQGTKVEIK	150
m2C1 LCDR1	RASRSISSWLA	151
m2C1 LCDR2	AASSLQS	148
m2C1 LCDR3	QQSYSIPAT	152
m2C1 VL	DIQMTQSPSSLSASVGDRVTITCRASRSISSWLAWYQQKPGK APKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQSYSIPATFGQGTKVEIK	153
m2A1 LCDR1	RASRGISSWLA	154
m2A1 LCDR2	AASSLQS	148
m2A1 LCDR3	QQSYSPPWT	155
m2A1 VL	DIQMTQSPSSLSASVGDRVTITCRASRGISSWLAWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSPPWTFGQGTKVEIK	156
m4A5 LCDR1	RASQSIDTWLA	157
m4A5 LCDR2	AASTLES	158
m4A5 LCDR3	QQSYRAPLT	159
m4A5 VL	DIQMTQSPSSLSASVGDRVTITCRASQSIDTWLAWYQQKPG KAPKLLIYAASTLESGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYRAPLTFGQGTKVEIK	160
m4D1 LCDR1	RASQSISAWLA	161
m4D1 LCDR2	KASSLES	162
m4D1 LCDR3	QQSYSPPAT	163
m4D1 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISAWLAWYQQKPG KAPKLLIYKASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSPPATFGGGTKVEIK	164
m3C6 LCDR1	RASQSIDTWLA	157
m3C6 LCDR2	EASSLQG	165
m3C6 LCDR3	QQSYSTWT	166
m3C6 VL	DIQMTQSPSSLSASVGDRVTITCRASQSIDTWLAWYQQKPG KAPKLLIYEASSLQGGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTWTFGQGTKVEIK	167
Heavy and light chains of 38B2 and m3A7		
38B2 full length HC (comprises 24H9 VH (SEQ ID NO: 24))	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQA PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCASSPLQWVDVWGQGTTVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(K)	168
38B2 HC (T350V/ T366L/ K392L/ T394W) LALAPG (comprises 24H9 VH (SEQ ID NO: 24))	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQA PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCASSPLQWVDVWGQGTTVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKRVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKF**N**WYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKAL**G**APIEKTISKAKGQPREPQVY***V***LPPSREEMTKNQVSL***L*** CLVKGFYPSDIAVEWESNGQPENNY***L***T***W***PPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(K)	169

TABLE 25-continued

Sequences of the disclosure

Identifier	Sequence	SEQ ID NO
38B2 full length LC (comprises 38B2 VL (SEQ ID NO: 98))	DIQMTQSPSSLSASVGDRVTITCRASESISSWLAWYQQKPGK APKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQGDSFPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC	170
m3A7 full length mHC LALAPG (comprises R3A9 VH (SEQ ID NO: 142))	QVQLVQSGAEVKKPGASVKVSCKASGHTFTSYYIHWVRQA PGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCARDRAYGGAGDYWGQGTLVTVSSAK TTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNS GSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVA HPASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPP KIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHT AQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNK DLGAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCM VTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYS KLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPG(K)	171
m3A7 mHC (L351Y/ F405A/ Y407V) LALAPG (comprises R3A9 VH (SEQ ID NO: 142))	QVQLVQSGAEVKKPGASVKVSCKASGHTFTSYYIHWVRQA PGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCARDRAYGGAGDYWGQGTLVTVSSAK TTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNS GSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVA HPASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPP KIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHT AQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNK DLGAPIERTISKPKGSVRAPQVYVYPPPEEEMTKKQVTLTCM VTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYAMVS KLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPG(K)	172
m3A7 full length mLC (comprises m3A7 VL (SEQ ID NO: 150))	DIQMTQSPSSLSASVGDRVTITCRASRSISNWLAWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSAPVTFGQGTKVEIKRADAAPTVSIFPPSSEQLT SGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQ DSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKS FNRNEC	173

Fusions of 38B2 heavy chains with SD15

hSD15 + 38B2 HC LALAPG (comprises 24H9 VH (SEQ ID NO: 24), linker 1 (SEQ ID NO: 215), and linker 2 (SEQ ID NO: 216))	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTS SLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSG GSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHI DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD TVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS FVHIVQMFINTSGGGGSGGGGSGGGGSGGGGSGGGGSGG GGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCASSPLQWVDVWGQGTTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPG(K)	174
hSD15 + 38B2HC (T350V/ L351Y/ F405A/ Y407V) LALAPG (comprises 24H9 VH (SEQ ID NO: 24), linker 1 (SEQ ID NO: 215), and linker 2 (SEQ ID NO: 216))	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTS SLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSG GSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHI DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD TVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS FVHIVQMFINTSGGGGSGGGGSGGGGSGGGGSGGGGSGG GGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCASSPLQWVDVWGQGTTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALGAPIEKTISKAKGQPREPQVYVVPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS	175

TABLE 25-continued

Sequences of the disclosure

Identifier	Sequence	SEQ ID NO
	FALVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPG(K)	
38B2HC LALAPG + hSD15 (comprises 24H9 VH (SEQ ID NO: 24) and linker 1 (SEQ ID NO: 215))	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQA PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCASSPLQWVDVWGQGTTVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGS **CPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSGGS GGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDA TLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTV ENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFV HIVQMFINTS**	176
38B2 HC (T350V/ L351Y/ F405A/ Y407V) LALAPG + hSD15 (comprises 24H9 VH (SEQ ID NO: 24) and linker 1 (SEQ ID NO: 215))	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQA PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCASSPLQWVDVWGQGTTVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALGAPIEKTISKAKGQPREPQVY**VY**PPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF**A**L**V** SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGS **CPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSGGS GGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDA TLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTV ENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFV HIVQMFINTS**	177
N65A hSD15+ 38B2 HC (T350V/ L351Y/ F405A/ Y407V) LALAPG (comprises 24H9 VH (SEQ ID NO: 24) and linker 1 (SEQ ID NO: 215), linker 1 (SEQ ID NO: 215), and linker 2 (SEQ ID NO: 216))	ITC**PPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTS SLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSG GSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHI DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD TVEALIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS FVHIVQMFINTS**GGGGGGGGGGGGGSGGGGGGGGGGG GGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCASSPLQWVDVWGQGTTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALGAPIEKTISKAKGQPREPQVY**VY**PPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FALVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPG(K)	178
N65D hSD15 + 38B2 HC (T350V/ L351Y/ F405A/ Y407V) LALAPG (comprises 24H9 VH (SEQ ID NO: 24), linker 1 (SEQ ID NO: 215), and linker 2 (SEQ ID N: 216))	ITC**PPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTS SLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSG GSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHI DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD TVEDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS FVHIVQMFINTS**GGGGSGGGGSGGGGSGGGGSGGGGSGG GGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCASSPLQWVDVWGQGTTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALGAPIEKTISKAKGQPREPQVY**VY**PPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FALVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPG(K)	179

TABLE 25-continued

Sequences of the disclosure

Identifier	Sequence	SEQ ID NO
N65S hSD15+	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTS	180
38B2 HC	SLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSG	
(T350V/	GSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHI	
L351Y/	DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD	
F405A/	TVESLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS	
Y407V)	FVHIVQMFINTSGGGGGGGGGGGGGSGGGGGGGGGGG	
LALAPG	GGS*EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQA*	
(comprises	*PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMN*	
24H9 VH (SEQ	*SLRAEDTAVYYCASSPLQWVDVWGQGTTVTVSS*	
ID NO: 24),	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW	
linker 1 (SEQ	NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC	
ID NO: 215),	NVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVF	
and linker 2	LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV	
(SEQ ID	EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC	
N: 216))	KVSNKALGAPIEKTISKAKGQPREPQVY**VY**PPSREEMTKNQ	
	VSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGS	
	F**A**L**V**SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL	
	SPG(K)	

Fusions of m3A7 heavy chains with SD15

mSD15 +	ITCPPPVSIEHADIRVKNYSVNSRERYVCNSGFKRKAGTST	181
m3A7 mHc	LIECVINKNTNVAHWTTPSLKCIRDPALVHQRPAPPSGGS	
LALAPG	GGGGSGGGSGGGGSLQNWIDVRYDLEKIESLIQSIHIDTT	
(comprises	LYTDSDFHPSCKVTAMNCFLLELQVILHEYSNMTLNETV	
R3A9 VH	RNVLYLANSTLSSNKNVAESGCKECEELEEKTFTEFLQSF	
(SEQ ID	IRIVQMFINTSGGGGSGGGGSGGGGSGGGGSGGGGSGGGG	
NO: 142), linker	SQVQLVQSGAEVKKPGASVKVSCKASGHTFTSYYIHWVRQ	
1 (SEQ ID	APGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVY	
NO: 215), and	MELSSLRSEDTAVYYCARDRAYGGAGDYWGQGTLVTVSSA	
linker 2 (SEQ	KTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNS	
ID N: 216))	GSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAH	
	PASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKI	
	KDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQ	
	TQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDL	
	GAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVT	
	DFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKL	
	RVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPG(K)	
mSD15 +	ITCPPPVSIEHADIRVKNYSVNSRERYVCNSGFKRKAGTST	182
m3A7 mHc	LIECVINKNTNVAHWTTPSLKCIRDPALVHQRPAPPSGGS	
(T366L/	GGGGSGGGSGGGGSLQNWIDVRYDLEKIESLIQSIHIDTT	
K392L/	LYTDSDFHPSCKVTAMNCFLLELQVILHEYSNMTLNETV	
T394W)	RNVLYLANSTLSSNKNVAESGCKECEELEEKTFTEFLQSF	
LALAPG	IRIVQMFINTSGGGGSGGGGSGGGGSGGGGSGGGGSGGGG	
(comprises	SQVQLVQSGAEVKKPGASVKVSCKASGHTFTSYYIHWVRQ	
R3A9 VH	APGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVY	
(SEQ ID	MELSSLRSEDTAVYYCARDRAYGGAGDYWGQGTLVTVSS	
NO: 142), linker	AKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTW	
1 (SEQ ID	NSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCN	
NO: 215), and	VAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIF	
linker 2 (SEQ	PPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVH	
ID N: 216))	TAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNN	
	KDLGAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTL**L**C	
	MVTDFMPEDIYVEWTNNGKTELNY**L**N**W**EPVLDSDGSYFM	
	YSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPG	
	(K)	
m3A7 mHc	QVQLVQSGAEVKKPGASVKVSCKASGHTFTSYYIHWVRQA	183
LALPG +	PGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYM	
mSD15	ELSSLRSEDTAVYYCARDRAYGGAGDYWGQGTLVTVSSAK	
(comprises	TTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNS	
R3A9 VH	GSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVA	
(SEQ ID	HPASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPP	
NO: 142) and	KIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHT	
linker 1 (SEQ	AQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNK	
ID NO: 215))	DLGAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCM	
	VTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYS	
	KLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGS**C**	
	PPPVSIEHADIRVKNYSVNSRERYVCNSGFKRKAGTSTLI	
	ECVINKNTNVAHWTTPSLKCIRDPALVHQRPAPPSGGSG	
	GGGSGGGSGGGGSLQNWIDVRYDLEKIESLIQSIHIDTTL	

TABLE 25-continued

Sequences of the disclosure

Identifier	Sequence	SEQ ID NO
	YTDSDFHPSCKVTAMNCFLLELQVILHEYSNMTLNETVR NVLYLANSTLSSNKNVAESGCKECEELEEKTFTEFLQSFI RIVQMFINTS	
m3A7 mHC (T366L/ K392L/ T394W) + mSD15 LALAPG (comprises R3A9 VH (SEQ ID NO: 142) and linker 1 (SEQ ID NO: 215))	QVQLVQSGAEVKKPGASVKVSCKASGHTFTSYYIHWVRQA PGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCARDRAYGGAGDYWGQGTLVTVSSAK TTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNS GSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVA HPASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPP KIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHT AQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNK DLGAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCM VTDFMPEDIYVEWTNNGKTELNYLNWEPVLDSDGSYFMYS KLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGSC **PPPVSIEHADIRVKNYSVNSRERYVCNSGFKRKAGTSTLI ECVINKNTNVAHWTTPSLKCIRDPALVHQRPAPPSGGSG GGGSGGGSGGGGSLQNWIDVRYDLEKIESLIQSIHIDTTL YTDSDFHPSCKVTAMNCFLLELQVILHEYSNMTLNETVR NVLYLANSTLSSNKNVAESGCKECEELEEKTFTEFLQSFI RIVQMFINTS**	184

Heavy and light chains of control antibody DP47 and fusions of DP47 heavy chains with SD15

DP47 mHC (L351Y/ F405A/ Y407V) LALAPG Residues 1-115: DP47 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAKGSGFDYWGQGTLVTVSSAKTTAPS VYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSS GVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASS TKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDV LMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQT HREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLGAP IERTISKPKGSVRAPQVYVYPPPEEEMTKKQVTLLCMVTDF MPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYAMVSKLRV EKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPG(K)	185
DP47 mLC Residues 1-108: DP47 VL	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPG QAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFA VYYCQQYGSSPLTFGQGTKVEIKRADAAPTVSIFPPSSEQLT SGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQ DSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKS FNRNEC	186
mSD15 + DP47 mHC LALAPG (comprises DP47 VH (see SEQ ID NO: 185), linker 1 (SEQ ID NO: 215), and linker 2 (SEQ ID N: 216))	IT**CPPPVSIEHADIRVKNYSVNSRERYVCNSGFKRKAGTS TLIECVINKNTNVAHWTTPSLKCIRDPALVHQRPAPPSG GSGGGGSGGGSGGGGSLQNWIDVRYDLEKIESLIQSIHID TTLYTDSDFHPSCKVTAMNCFLLELQVILHEYSNMTLNE TVRNVLYLANSTLSSNKNVAESGCKECEELEEKTFTEFL QSFIRIVQMFINTS**GGGGSGGGGSGGGGSGGGGSGGGSG GGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWV RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCAKGSGFDYWGQGTLVTVSSAK TTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNS GSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVA HPASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPP KIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHT AQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNK DLGAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCM VTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYS KLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPG(K)	187
mSD15 + DP47 mHC (T366L/ K392L/ T394W) LALAPG (comprises DP47 VH (see SEQ ID	IT**CPPPVSIEHADIRVKNYSVNSRERYVCNSGFKRKAGTST LIECVINKNTNVAHWTTPSLKCIRDPALVHQRPAPPSGGS GGGGSGGGSGGGGSLQNWIDVRYDLEKIESLIQSIHIDTT LYTDSDFHPSCKVTAMNCFLLELQVILHEYSNMTLNETV RNVLYLANSTLSSNKNVAESGCKECEELEEKTFTEFLQSF IRIVQMFINTS**GGGGSGGGGSGGGGSGGGGSGGGSGGGG SEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQA PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCAKGSGFDYWGQGTLVTVSSAKTTA	188

TABLE 25-continued

Sequences of the disclosure

Identifier	Sequence	SEQ ID NO
NO: 185), linker 1 (SEQ ID NO: 215), and linker 2 (SEQ ID N: 216))	PSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSL SSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPA SSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKD VLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQ THREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLGA PIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLLCMVTDF MPEDIYVEWTNNGKTELNYLNWEPVLDSDGSYFMYSKLRV EKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPG(K)	
DP47 mHc LALAPG + mSD15 (comprises DP47 VH (see SEQ ID NO: 185) and linker 1 (SEQ ID NO: 215))	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAKGSGFDYWGQGTLVTVSSAKTTAPS VYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSS GVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASS TKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDV LMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQT HREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLGAP IERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDF MPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRV EKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGS**CPPPVS** **IEHADIRVKNYSVNSRERYVCNSGFKRKAGTSTLIECVIN** **KNTNVAHWTTPSLKCIRDPALVHQRPAPPSGGSGGGGGS** **GGGSGGGGSLQNWIDVRYDLEKIESLIQSIHIDTTLYTDS** **DFHPSCKVTAMNCFLLELQVILHEYSNMTLNETVRNVLY** **LANSTLSSNKNVAESGCKECEELEEKTFTEFLQSFIRIVQ** **MFINTS**	189
DP47 mHC (T366L/ K392L/ T394W) LALAPG + mSD15 (comprises DP47 VH (see SEQ ID NO: 185) and linker 1 (SEQ ID NO: 215))	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAKGSGFDYWGQGTLVTVSSAKTTAPS VYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSS GVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASS TKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDV LMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQT HREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLGAP IERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLLCMVTDF MPEDIYVEWTNNGKTELNYLNWEPVLDSDGSYFMYSKLRV EKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGS**CPPPVS** **IEHADIRVKNYSVNSRERYVCNSGFKRKAGTSTLIECVIN** **KNTNVAHWTTPSLKCIRDPALVHQRPAPPSGGSGGGGSG** **GGSGGGGSLQNWIDVRYDLEKIESLIQSIHIDTTLYTDSDF** **HPSCKVTAMNCFLLELQVILHEYSNMTLNETVRNVLYLA** **NSTLSSNKNVAESGCKECEELEEKTFTEFLQSFIRIVQMFI** **NTS**	190
DP47 HC (T350V/ T366L/ K392L/ T394W) LALAPG (comprises DP47 VH (see SEQ ID NO: 185))	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAKGSGFDYWGQGTLVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYVLPPSREEMTKNQVSLLCLVK GFYPSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(K)	191
DP47 LC Residues 1-108: DP47 VL	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPG QAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFA VYYCQQYGSSPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC	192
hSD15 + DP47 HC LALPG (comprises DP47 VH (see SEQ ID NO: 185), linker 1 (SEQ ID NO: 215), and linker 2 (SEQ ID N: 216))	ITC**PPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTS** **SLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSG** **GSGGGGSGGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHI** **DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD** **TVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS** **FVHIVQMFINTS**GGGGSGGGGSGGGGSGGGGSGGGGSGG GGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVR QAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCAKGSGFDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPP	193

TABLE 25-continued

Sequences of the disclosure

Identifier	Sequence	SEQ ID NO
	KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(K)	
hSD15 + DP47 HC (T350V/ L351Y/ F405A/ Y407V) LALAPG (comprises DP47 VH (see SEQ ID NO: 185), linker 1 (SEQ ID NO: 215), and linker 2 (SEQ ID N: 216))	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTS SLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSG GSGGGGSGGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHI DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD TVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS FVHIVQMFINTSGGGGGGGGGGGGSGGGGGGGGGGG GGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVR QAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCAKGSGFDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALGAPIEKTISKAKGQPREPQVYVYPPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFALV SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(K)	194
DP47 HC + LALAPG hSD15 (comprises DP47 VH (see SEQ ID NO: 185) and linker 1 (SEQ ID NO: 215))	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAKGSGFDYWGQGTLVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGS**CPPPM** **SVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVL** **NKATNVAHWTTPSLKCIRDPALVHQRPAPPSGGSGGGG** **SGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDATLYT** **ESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII** **LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQ** **MFINTS**	195
DP47 HC (T350V/ L351Y/ F405A/ Y407V) LALAPG + hSD15 (comprises DP47 VH (see SEQ ID NO: 185) and linker 1 (SEQ ID NO: 215)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAKGSGFDYWGQGTLVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYVYPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFALVSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGS**CPPP** **MSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTEC** **VLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSGGSGG** **GGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDATL** **YTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEN** **LIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHI** **VQMFINTS**	196
N65A-hSD15 + DP47 HC (T350V/ L351Y/ F405A/ Y407V) LALAPG (comprises DP47 VH (see SEQ ID NO: 185), linker 1 (SEQ ID NO: 215), and linker 2 (SEQ ID N: 216))	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTS SLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSG GSGGGGSGGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHI DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD TVEALIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS FVHIVQMFINTSGGGGSGGGGSGGGGSGGGGSGGGGSGG *GGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQA* *PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMN* *SLRAEDTAVYYCAKGSGFDYWGQGTLVTVSS*ASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEK TISKAKGQPREPQVYVYPPSREEMTKNQVSLTCLVKGFYPS	197

TABLE 25-continued

Sequences of the disclosure

Identifier	Sequence	SEQ ID NO
	DIAVEWESNGQPENNYKTTPPVLDSDGSFALVSKLTVDKSR	
	WQQGNVFSCSVMHEALHNHYTQKSLSLSPG(K)	
N65D-hSD15 +	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTS	198
DP47 HC	SLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSG	
(T350V/	GSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHI	
L351Y/	DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD	
F405A/Y407V)	TVEDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS	
LALAPG	FVHIVQMFINTSGGGGSGGGGSGGGGSGGGGSGGGGSGG	
(comprises	GGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVR	
DP47 VH (see	QAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTL	
SEQ ID	YLQMNSLRAEDTAVYYCAKGSGFDYWGQGTLVTVSSAST	
NO: 185), linker	KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG	
1 (SEQ ID	ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN	
NO: 215), and	HKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPP	
linker 2 (SEQ	KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH	
ID N: 216))	NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS	
	NKALGAPIEKTISKAKGQPREPQVYVYPPSREEMTKNQVSLT	
	CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFALV	
	SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(K)	
N65S-hSD15 +	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTS	199
DP47 HC	SLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSG	
(T350V/	GSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHI	
L351Y/	DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD	
F405A/	TVESLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS	
Y407V)	FVHIVQMFINTSGGGGSGGGGSGGGGSGGGGSGGGGSGG	
LALAPG	GGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVR	
(comprises	QAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTL	
DP47 VH (see	YLQMNSLRAEDTAVYYCAKGSGFDYWGQGTLVTVSSAST	
SEQ ID	KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG	
NO: 185), linker	ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN	
1 (SEQ ID	HKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPP	
NO: 215) and	KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH	
linker 2 (SEQ	NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS	
ID N: 216))	NKALGAPIEKTISKAKGQPREPQVYVYPPSREEMTKNQVSLT	
	CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFALV	
	SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(K)	

Heavy and light chains of anti-PD-L1 antibody D7A8 and fusions of D7A8 heavy chains with SD15

D7A8 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSAYRMFWVRQA	200
	PGKGLEWVSSIYPSGGITFYADSVKGRFTISRDNSKNTLYLQ	
	MNSLRAEDTAIYYCARIKLGTVTTVDYWGQGTLVTVSS	
D7A8 full	EVQLLESGGGLVQPGGSLRLSCAASGFTFSAYRMFWVRQA	201
length HC	PGKGLEWVSSIYPSGGITFYADSVKGRFTISRDNSKNTLYLQ	
(comprises	MNSLRAEDTAIYYCARIKLGTVTTVDYWGQGTLVTVSSAST	
D7A8 VH	KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG	
(SEQ ID	ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN	
NO: 200))	HKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP	
	KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH	
	NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS	
	NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT	
	CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY	
	SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(K)	
D7A8 HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSAYRMFWVRQA	202
(S354C/	PGKGLEWVSSIYPSGGITFYADSVKGRFTISRDNSKNTLYLQ	
T366W)	MNSLRAEDTAIYYCARIKLGTVTTVDYWGQGTLVTVSSAST	
LALA	KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG	
(comprises	ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN	
D7A8 VH	HKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPP	
(SEQ ID	KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH	
NO: 200))	NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS	
	NKALPAPIEKTISKAKGQPREPQVYTLPPCREEMTKNQVSL	
	WCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL	
	YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	
	(K)	
D7A8 HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSAYRMFWVRQA	203
(T350V/	PGKGLEWVSSIYPSGGITFYADSVKGRFTISRDNSKNTLYLQ	
T366L/	MNSLRAEDTAIYYCARIKLGTVTTVDYWGQGTLVTVSSAST	
K392L/	KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG	
T394W)	ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN	

TABLE 25-continued

Sequences of the disclosure

Identifier	Sequence	SEQ ID NO
LALA (comprises D7A8 VH SEQ ID NO: 200))	HKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYVLPPSREEMTKNQVSLL CLVKGFYPSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(K)	
D7A8 VL	QSALTQPASVSGSPGQSITISCTGTSSDVGAYNYVSWYQQHP GKAPKLMIYDVSNRPSGVSNRFSGSKSGNTASLTISGLQAED EADYYCSSYTSSSTRVFGTGTKVTVLGQP	204
D7A8 full length LC (comprises D7A8 VL (SEQ ID NO: 204))	QSALTQPASVSGSPGQSITISCTGTSSDVGAYNYVSWYQQHP GKAPKLMIYDVSNRPSGVSNRFSGSKSGNTASLTISGLQAED EADYYCSSYTSSSTRVFGTGTKVTVLGQPKANPTVTLFPPSS EELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETT KPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVE KTVAPTEC(S)	205
hSD15 + D7A8 HC LALA (comprises D7A8 VH (SEQ ID NO: 200), linker 1 (SEQ ID NO: 215), and the linker of SEQ ID N: 244)	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTS SLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSG GSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHI DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD TVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS FVHIVQMFINTSGGGGGGGGGGGGSGGGGSEVQLLESG GGLVQPGGSLRLSCAASGFTFSAYRMFWVRQAPGKGLEWV SSIYPSGGITFYADSVKGRFTISRDNSKNTLYLQMNSLRAED TAIYYCARIKLGTVTTVDYWGQGTLVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPG(K)	206
hSD15 + D7A8HC (Y349C/ T366S/ L368A/ Y407V) LALA (comprises D7A8 VH (SEQ ID NO: 200), linker 1 (SEQ ID NO: 215), and the linker of SEQ ID N: 244))	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTS SLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSG GSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHI DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD TVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS FVHIVQMFINTSGGGGSGGGGSGGGGSGGGGSEVQLLESG GGLVQPGGSLRLSCAASGFTFSAYRMFWVRQAPGKGLEWV SSIYPSGGITFYADSVKGRFTISRDNSKNTLYLQMNSLRAED TAIYYCARIKLGTVTTVDYWGQGTLVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVCTLPPSREEMTKNQVSLSCAVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPG(K)	207
hSD15 + D7A8HC (T350V/ L351Y/ F405A/ Y407V) LALA (comprises D7A8 VH (SEQ ID NO: 200), linker 1 (SEQ ID NO: 215), and the linker of SEQ ID N: 244))	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTS SLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSG GSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHI DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD TVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS FVHIVQMFINTSGGGGSGGGGSGGGGSGGGGSEVQLLESG GGLVQPGGSLRLSCAASGFTFSAYRMFWVRQAPGKGLEWV SSIYPSGGITFYADSVKGRFTISRDNSKNTLYLQMNSLRAED TAIYYCARIKLGTVTTVDYWGQGTLVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVVYPPSREEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFALVSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(K)	208
D7A8 HC LALA + hSD15 (comprises D7A8 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSAYRMFWVRQA PGKGLEWVSSIYPSGGITFYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAIYYCARIKLGTVTTVDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN	209

TABLE 25-continued

Sequences of the disclosure

Identifier	Sequence	SEQ ID NO
(SEQ ID NO: 200) and linker 1 (SEQ ID NO: 215))	HKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGS **CPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSL** **TECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSGGS** **GGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDA** **TLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTV** **ENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFV** **HIVQMFINTS**	
D7A8 HC (Y349C/ T366S/ L368A/ Y407V) LALA+ hSD15 (comprises D7A8 VH (SEQ ID NO: 200) and linker 1 (SEQ ID NO: 215))	EVQLLESGGGLVQPGGSLRLSCAASGFTFSAYRMFWVRQA PGKGLEWVSSIYPSGGITFYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAIYYCARIKLGTVTTVDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQV**C**TLPPSREEMTKNQVSL**S** C**A**VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL**V** SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG**C** **PPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLT** **ECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSGGSG** **GGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDAT** **LYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVE** **NLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFV** **HIVQMFINTS**	210
D7A8 HC (T350V/ L351Y/ F405A/ Y407V) LALA + hSD15 (comprises D7A8 VH (SEQ ID NO: 200) and linker 1 (SEQ ID NO: 215))	EVQLLESGGGLVQPGGSLRLSCAASGFTFSAYRMFWVRQA PGKGLEWVSSIYPSGGITFYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAIYYCARIKLGTVTTVDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQV**YY**PPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF**A**L**V** SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG**C** **PPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLT** **ECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSGGSG** **GGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDAT** **LYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVE** **NLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFV** HIVQMFINTS	211

IL-15 and IL-15 Rα sequences

Human IL-15 (mature protein, residue N65 is in bold)	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMK CFLLELQVISLESGDASIHDTVE**N**LIILANNSLSSNGNVTESG CKECEELEEKNIKEFLQSFVHIVQMFINTS	212
Human IL-15 Rα subunit (signal peptide is underlined, residue N60 is in bold)	MAPRRARGCRTLGLPALLLLLLLRPPATRGITCPPPMSVEHA DIWVKSYSLYSRERYIC**N**SGFKRKAGTSSLTECVLNKATNV AHWTTPSLKCIRDPALVHQRPAPPSTVTTAGVTPQPESLSPS GKEPAASSPSSNNTAATTAAIVPGSQLMPSKSPSTGTTEISSH ESSHGTPSQTTAKNWELTASASHQPPGVYPQHSDTTVAISTS TVLLCGLSAVSLLACYLKSRQTPPLASVEMEAMEALPVTW GTSSRDEDLENCSHHL	213
IL-15Rα sushi domain (residue corresponding to residue N60 in SEQ ID NO: 213 is shown in bold)	CPPPMSVEHADIWVKSYSLYSRERYIC**N**SGFKRKAGTSSLTE CVLNKATNVAHWTTPSLKC	214

TABLE 25-continued

Sequences of the disclosure

Identifier	Sequence	SEQ ID NO
	Linker sequences	
Linker 1	IRDPALVHQRPAPPSGGSGGGGSGGGSGGGGSLQ	215
Linker 2	GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS	216
Exemplary linker	IRDPSGGGGSGGGGSGGGGSGGGGSGGGGSGGGG	217
Exemplary linker	IRDPGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS	218
Exemplary linker	GGGGSGGGGSGGGGSGGGGS	244

VH: heavy variable chain
HC: (full length) heavy chain
VL: light variable chain
LC: (full length) light chain
mHC: murine (full length) heavy chain
mLC: murine (full length) light chain
SD15: bold
LALA/LALAPG substitution: underlined (not bold)
Substitution to stabilize heterodimer of two heavy chains: bold, underlight, italics
Linkers: underlined
Amino acid substitutions in IL-15: double underlined
(K): optional lysine reside

TABLE 26

Sequences of the disclosure

Name	Dimer of HC	Light chain	Fc amino acid substitution type for heterodimer	Heavy chain 1	Heavy chain 2 (with IL-15)
2N_D7A8_hIL-15	homo	205	none	none	206
1N_D7A8_hIL-15	hetero	205	Knobs-into-holes (CW-CSAV)	202	207
			ZW1 (VYAV-VLLW)	203	208
2C_D7A8_hIL-15	homo	205	none	none	209
1C_D7A8_hIL-15	hetero	205	Knobs-into-holes (CW-CSAV)	202	210
			ZW1 (VYAV-VLLW)	203	211
2N_DP47_mIL-15	homo	186	none	none	187
1N_DP47_mIL-15	hetero	186	Modified ZW1 (VYAV-VLLW)	185	188
2C_DP47_mIL-15	homo	186	none	none	189
1C_DP47_mIL-15	hetero	186	Modified ZW1 (VYAV-VLLW)	185	190
2N_m3A7_mIL-15	homo	173	none	none	181
1N_m3A7_mIL-15	hetero	173	Modified ZW1 (VYAV-VLLW)	172	182
2C_m3A7_mIL-15	homo	173	none	none	183
1C_m3A7_mIL-15	hetero	173	Modified ZW1 (VYAV-VLLW)	172	184
2N_38B2_hIL-15	homo	170	none	none	174
1N_38B2_hIL-15	hetero	170	ZW1 (VYAV-VLLW)	169	175
2C_38B2_hIL-15	homo	170	none	none	176
1C_38B2_hIL-15	hetero	170	ZW1 (VYAV-VLLW)	169	177
2N_DP47_hIL-15	homo	192	none	none	193
1N_DP47_hIL-15	hetero	192	ZW1 (VYAV-VLLW)	191	194
2C_DP47_hIL-15	homo	192	none	none	195
1C_DP47_hIL-15	hetero	192	ZW1 (VYAV-VLLW)	191	196
N65A_1N_38B2_hIL-15	hetero	170	ZW1 (VYAV-VLLW)	169	178
N65D_1N_38B2_hIL-15	hetero	170	ZW1 (VYAV-VLLW)	169	179
N65S_1N_38B2_hIL-15	hetero	170	ZW1 (VYAV-VLLW)	169	180
N65A_1N_DP47_IL-15	hetero	192	ZW1 (VYAV-VLLW)	191	197
N65D_1N_DP47_hIL-15	hetero	192	ZW1 (VYAV-VLLW)	191	198
N65S_1N_DP47_hIL-15	hetero	192	ZW1 (VYAV-VLLW)	191	199

TABLE 27

Exemplary embodiments of fusion proteins comprising antibody 38B2. All fusion proteins in this table comprise the light chain of 38B2. The individual sequences referenced in this table are provided in Table 28. As an example, in 1N-38B2_1, the first heavy chain comprises heterodimerization amino acid substitutions T350V/T366L/K392L/T394W and the second heavy chain comprises heterodimerization amino acid substitutions T350V/L351Y/F405A/Y407V. In 1N-38B2_2, the first heavy chain comprises heterodimerization amino acid substitutions T350V/L351Y/F405A/Y407V and the second heavy chain comprises heterodimerization amino acid substitutions T350V/T366L/K392L/T394W.

Fusion protein name	Heavy chain 1 (HC1) SEQ ID NO	Heavy chain 1 (HC1) Name	Heavy chain 2 (HC2) SEQ ID NO:	Heavy chain 2 (HC2) Name	Linker between IL-15Rα sushi and IL-15	Fc engineering Effector region	Fc engineering Heterodimerization
1N-38B2_1	220	38B2HC1-1	224	65N-38B2HC2-1	SGGSGGGGSGGGSGGGGSLQ	LALAPG	ZW1
1N-38B2_2	221	38B2HC1-2	225	65N-38B2HC2-2	SGGSGGGGSGGGSGGGGSLQ		(VYAV-VLLW)
1N-38B2_3	222	38B2HC1-3	226	65N-38B2HC2-3	SGGSGGGGSGGGSGGGGSLQ		Knobs-into-holes
1N-38B2_4	223	38B2HC1-4	227	65N-38B2HC2-4	SGGSGGGGSGGGSGGGGSLQ		(CW-CSAV)
65S-38B2_1	220	38B2HC1-1	228	65S-38B2HC2-1	SGGSGGGGSGGGSGGGGSLQ	LALAPG	ZW1
65S-38B2_2	221	38B2HC1-2	229	65S-38B2HC2-2	SGGSGGGGSGGGSGGGGSLQ		(VYAV-VLLW)
65S-38B2_3	222	38B2HC1-3	230	65S-38B2HC2-3	SGGSGGGGSGGGSGGGGSLQ		Knobs-into-holes
65S-38B2_4	223	38B2HC1-4	231	65S-38B2HC2-4	SGGSGGGGSGGGSGGGGSLQ		(CW-CSAV)
65S-38B2_5	220	38B2HC1-1	236	65S-38B2HC2-5	SGGGGSGGGGSGGGSGGGGS	LALAPG	ZW1
65S-38B2_6	221	38B2HC1-2	237	65S-38B2HC2-6	SGGGGSGGGGSGGGSGGGGS		(VYAV-VLLW)
65S-38B2_7	222	38B2HC1-3	238	65S-38B2HC2-7	SGGGGSGGGGSGGGSGGGGS		Knobs-into-holes
65S-38B2_8	223	38B2HC1-4	239	65S-38B2HC2-8	SGGGGSGGGGSGGGSGGGGS		(CW-CSAV)
65D-38B2_1	220	38B2HC1-1	232	65D-38B2HC2-1	SGGSGGGGSGGGSGGGGSLQ	LALAPG	ZW1
65D-38B2_2	221	38B2HC1-2	233	65D-38B2HC2-2	SGGSGGGGSGGGSGGGGSLQ		(VYAV-VLLW)
65D-38B2_3	222	38B2HC1-3	234	65D-38B2HC2-3	SGGSGGGGSGGGSGGGGSLQ		Knobs-into-holes
65D-38B2_4	223	38B2HC1-4	235	65D-38B2HC2-4	SGGSGGGGSGGGSGGGGSLQ		(CW-CSAV)
65S-38B2_9	240	38B2HC1-3B	241	65S-38B2HC2-3B	SGGSGGGGSGGGSGGGGSLQ	LALA	Knobs-into-holes (CW-CSAV)
65S-38B2_10	240	38B2HC1-3B	242	65S-38B2HC2-7B	SGGGGSGGGGSGGGSGGGGS		Knobs-into-holes (CW-CSAV)
65D-38B2_5	240	38B2HC1-3B	243	65D-38B2HC2-3B	SGGSGGGGSGGGSGGGGSLQ		Knobs-into-holes (CW-CSAV)

TABLE 28

Sequences for fusion protein embodiments provided in Table 27.

SEQ ID NO:	Name	Amino acid sequence
219	38B2 LC (comprises 38B2 VL (SEQ ID NO: 98))	**DIQMTQSPSSLSASVGDRVTITCRASESISSWLAWYQQKPGKAPKLLIYDASSLESGVPSRFSGS** **GSGTDFTLTISSLQPEDFATYYCQQGDSFPFTFGQGTKLEIK**RTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV THQGLSSPVTKSFNRGEC
220	38B2 HC1-1 (T350V/ T366L/ K392L/ T394W) LALAPG	**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVSAISGSGGSTYYAD** **SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSPLQWVDVWGQGTTVTVSS**ASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKAL**G**APIEKTISKAKGQPREPQVY**V**LPPSRDELTKNQVSL**L**CLVKGFYPSDIAVEWESNGQPENNY **L**T**W**PPVLDSDGSFFLYSKLTVDKSR**W**QQGNVFSCSVMHEAL**H**NHYTQKSLSLSPGK
221	38B2 HC1-2 (T350V/ L351Y/ F405A/ Y407V) LALAPG	**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVSAISGSGGSTYYAD** **SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSPLQWVDVWGQGTTVTVSS**ASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKAL**G**APIEKTISKAKGQPREPQVY**VY**PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSF**AL**VSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
222	38B2 HC1-3 (CW-CSAV) S354C/ T366W LALAPG	**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVSAISGSGGSTYYAD** **SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSPLQWVDVWGQGTTVTVSS**ASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS

TABLE 28-continued

Sequences for fusion protein embodiments provided in Table 27.

SEQ ID NO:	Name	Amino acid sequence
		NKAL***G***APIEKTISKAKGQPREPQVYTLPP**C**RDELTKNQVSL**W**CLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
223	38B2 HC1-4 (CW-CSAV) Y349C/ T366S/ L368A/ Y407V LALAPG	**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVSAISGSGGSTYYAD** **SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSPLQWVDVWGQGTTVTVSS**ASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE***AA***GGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKAL***G***APIEKTISKAKGQPREPQV**C**TLPPSRDELTKNQVSL**S**C**A**VKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFL**V**SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
224	65N-38B2 HC2-1 (T350V/ L351Y/ F405A/ Y407V) LALAPG	*ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQ* *RPAPPSGGSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL* *ELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS*GGGG SGGGGSGGGGSGGGGSGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSP LQWVDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP E***AA***GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL***G***APIEKTISKAKGQPREPQVYVYPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFALVSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK
225	65N-38B2 HC2-2 (T350V/ T366L/ K392L/ T394W) LALAPG	*ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQ* *RPAPPSGGSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL* *ELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS*GGGG SGGGGSGGGGSGGGGSGGGGSGGGGS**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV** **RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSP** **LQWVDVWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP E***AA***GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL***G***APIEKTISKAKGQPREPQVY**V**LPPSRDELTKNQVS L**L**CLVKGFYPSDIAVEWESNGQPENNY**L**T**W**PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK
226	65N-38B2 HC2-3 (CW-CSAV) Y349C/ T366S/ L368A/ Y407V LALAPG	*ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQ* *RPAPPSGGSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL* *ELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS*GGGG SGGGGSGGGGSGGGGSGGGGSGGGGS**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV** **RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSP** **LQWVDVWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP E***AA***GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL***G***APIEKTISKAKGQPREPQV**C**TLPPSRDELTKNQVS L**S**C**A**VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL**V**SKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK
227	65N-38B2 HC2-4 S354C/ T366W LALAPG	*ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQ* *RPAPPSGGSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL* *ELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS*GGGG SGGGGSGGGGSGGGGSGGGGSGGGGS**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV** **RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSP** **LQWVDVWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP E***AA***GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL***G***APIEKTISKAKGQPREPQVYTLPP**C**RDELTKNQVS L**W**CLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ**Q**GNVFSCSVMH EALHNHYTQKSLSLSPGK
228	65S-38B2 HC2-1 (T350V/ L351Y/ F405A/ Y407V) LALAPG	*ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQ* *RPAPPSGGSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL* *ELQVISLESGDASIHDTVESLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS*GGGG SGGGGSGGGGSGGGGSGGGGSGGGGS**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV** **RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSP** **LQWVDVWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP E***AA***GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL***G***APIEKTISKAKGQPREPQVYVYPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFALVSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK

TABLE 28-continued

Sequences for fusion protein embodiments provided in Table 27.

SEQ ID NO:	Name	Amino acid sequence
229	65S-38B2 HC2-2 (T350V/ T366L/ K392L/ T394W) LALAPG	*ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQ* *RPAPPSGGSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL* *ELQVISLESGDASIHDTVESLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGG* SGGGGSGGGGSGGGGSGGGGSGGGGS**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV** **RQAPGKGLEWVSAISGSGGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSP** **LQWVDVWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP E**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL***G***APIEKTISKAKGQPREPQVY**V**LPPSRDELTKNQVS L**L**CLVKGFYPSDIAVEWESNGQPENNY**L**T**W**PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK
230	65S-38B2 HC2-3 (CW-CSAV) Y349C/ T366S/ L368A/ Y407V LALAPG	*ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQ* *RPAPPSGGSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL* *ELQVISLESGDASIHDTVESLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGG* SGGGGSGGGGSGGGGSGGGGSGGGGS**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV** **RQAPGKGLEWVSAISGSGGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSP** **LQWVDVWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP E**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL***G***APIEKTISKAKGQPREPQV**C**TLPPSRDELTKNQVS L**S**C**A**VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL**V**SKLTVDK**S**RWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK
231	65S-38B2 HC2-4 S354C/ T366W LALAPG	*ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQ* *RPAPPSGGSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL* *ELQVISLESGDASIHDTVESLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGG* SGGGGSGGGGSGGGGSGGGGSGGGGS**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV** **RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSP** **LQWVDVWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP E**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL***G***APIEKTISKAKGQPREPQVYTLPP**C**RDELTKNQVS L**W**CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK
232	65D-38B2 HC2-1 (T350V/ L351Y/ F405A/ Y407V) LALAPG	*ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQ* *RPAPPSGGSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL* *ELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGG* SGGGGSGGGGSGGGGSGGGGSGGGGS**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV** **RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSP** **LQWVDVWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP E**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL***G***APIEKTISKAKGQPREPQVY**VY**PPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF**A**L**V**SKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK
233	65D-38B2 HC2-2 (T350V/ T366L/ K392L/ T394W) LALAPG	*ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQ* *RPAPPSGGSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL* *ELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGG* SGGGGSGGGGSGGGGSGGGGSGGGGS**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV** **RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSP** **LQWVDVWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP E**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL***G***APIEKTISKAKGQPREPQVY**V**LPPSRDELTKNQVS L**L**CLVKGFYPSDIAVEWESNGQPENNY**L**T**W**PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK
234	65D-38B2 HC2-3 (CW-CSAV) Y349C/ T366S/ L368A/ Y407V LALAPG	*ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQ* *RPAPPSGGSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL* *ELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGG* SGGGGSGGGGSGGGGSGGGGSGGGGS**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV** **RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSP** **LQWVDVWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP E**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL***G***APIEKTISKAKGQPREPQV**C**TLPPSRDELTKNQVS L**S**C**A**VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL**V**SKLTVDK**S**RWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK

TABLE 28-continued

Sequences for fusion protein embodiments provided in Table 27.

SEQ ID NO:	Name	Amino acid sequence
235	65D-38B2 HC2-4 S354C/ T366W LALAPG	*ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQ* *RPAPPSGGSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL* *ELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS*GGGG SGGGGSGGGGSGGGGSGGGGSGGGGS**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV** **RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSP** **LQWVDVWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP E**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL***G***APIEKTISKAKGQPREPQVYTLPP**C**RDELTKNQVS L**W**CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK
236	65S-38B2 HC2-5 (T350V/ L351Y/ F405A/ Y407V) LALAPG	*ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQ* *RPAPPSGGGGSGGGGSGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL* *ELQVISLESGDASIHDTVESLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS*GGGG SGGGGSGGGGSGGGGSGGGGSGGGGS**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV** **RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSP** **LQWVDVWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP E**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL***G***APIEKTISKAKGQPREPQVY**VY**PPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF**A**L**V**SKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK
237	65S-38B2 HC2-6 (T350V/ T366L/ K392L/ T394W) LALAPG	*ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQ* *RPAPPSGGGGSGGGGSGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL* *ELQVISLESGDASIHDTVESLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS*GGGG SGGGGSGGGGSGGGGSGGGGSGGGGS**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV** **RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSP** **LQWVDVWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP E**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL***G***APIEKTISKAKGQPREPQVY**V**LPPSRDELTKNQVS L**L**CLVKGFYPSDIAVEWESNGQPENNY**L**T**W**PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK
238	65S-38B2 HC2-7 (CW-CSAV) Y349C/ T366S/ L368A/ Y407V LALAPG	*ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQ* *RPAPPSGGGGSGGGGSGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL* *ELQVISLESGDASIHDTVESLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS*GGGG SGGGGSGGGGSGGGGSGGGGSGGGGS**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV** **RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSP** **LQWVDVWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP E**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL***G***APIEKTISKAKGQPREPQV**C**TLPPSRDELTKNQVS L**S**C**A**VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL**V**SKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK
239	65S-38B2 HC2-8 S354C/ T366W LALAPG	*ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQ* *RPAPPSGGGGSGGGGSGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL* *ELQVISLESGDASIHDTVESLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS*GGGG SGGGGSGGGGSGGGGSGGGGSGGGGS**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV** **RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSP** **LQWVDVWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP E**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL***G***APIEKTISKAKGQPREPQVYTLPP**C**RDELTKNQVS L**W**CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK
240	38B2 HC1-3B (CW-CSAV) S354C/ T366W LALA	**EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVSAISGSGGSTYYAD** **SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSPLQWVDVWGQGTTVTVSS**ASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKAL**P**APIEKTISKAKGQPREPQVYTLPP**C**RDELTKNQVSL**W**CLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

TABLE 28-continued

Sequences for fusion protein embodiments provided in Table 27.

SEQ ID NO:	Name	Amino acid sequence
241	65S-38B2 HC2-3B (CW-CSAV) Y349C/ T366S/ L368A/ Y407V/ LALA	*ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQ* *RPAPPSGGSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL* *ELQVISLESGDASIHDTVESLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGG* *SGGGGSGGGGSGGGGSGGGGSGGGGS***EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV** **RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSP** **LQWVDVWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP E**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL**P**APIEKTISKAKGQPREPQV**C**TLPPSRDELTKNQVS L**S**C**A**VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL**V**SKLTVDK**S**RWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK
242	65S-38B2 HC2-7B (CW-CSAV) Y349C/ T366S/ L368A/ Y407V/ LALA	*ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQ* *RPAPPSGGGGSGGGGSGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL* *ELQVISLESGDASIHDTVESLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGG* *SGGGGSGGGGSGGGGSGGGGSGGGGS***EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV** **RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSP** **LQWVDVWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP E**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL**P**APIEKTISKAKGQPREPQV**C**TLPPSRDELTKNQVS L**S**C**A**VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL**V**SKLTVDK**S**RWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK
243	65D-38B2 HC2-3B (CW-CSAV) Y349C/ T366S/ L368A/ Y407V/ LALA	*ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQ* *RPAPPSGGSGGGGSGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL* *ELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGG* *SGGGGSGGGGSGGGGSGGGGSGGGGS***EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWV** **RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSP** **LQWVDVWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP E**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL**P**APIEKTISKAKGQPREPQV**C**TLPPSRDELTKNQVS L**S**C**A**VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL**V**SKLTVDK**S**RWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK

Variable chains are in bold (not underlined). LALAPG and LALA amino acid substitutions are indicated in bold and italics. Amino acid substitutions relating to heterodimerization are indicated in bold and underlined. The SD15 portion is shown in italics. Linker regions are indicated in italics and underlined. All 38B2 HC comprise 24H9 VH (SEQ ID NO: 24).

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 244

<210> SEQ ID NO 1
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19B6 HCDR1

<400> SEQUENCE: 1

Gly Tyr Thr Phe Thr Gly Tyr Tyr Met His
1 5 10

<210> SEQ ID NO 2
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19B6 HCDR2

<400> SEQUENCE: 2

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Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> SEQ ID NO 3
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19B6 HCDR3

<400> SEQUENCE: 3

Thr Ala Gly Tyr Asp Trp Leu Pro Ser Gly Leu Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 4
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19B6 VH

<400> SEQUENCE: 4

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Thr Ala Gly Tyr Asp Trp Leu Pro Ser Gly Leu Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 5
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19B10 HCDR1

<400> SEQUENCE: 5

Gly Phe Thr Phe Ser Ser Tyr Ala Met His
1 5 10

<210> SEQ ID NO 6
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19B10 HCDR2

<400> SEQUENCE: 6

Gly Ile Ser Asn Ser Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val Lys

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1 5 10 15

Gly

<210> SEQ ID NO 7
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19B10 HCDR3

<400> SEQUENCE: 7

Asp Asn Tyr Tyr Tyr Tyr Met Asp Val
1 5

<210> SEQ ID NO 8
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19B10 VH

<400> SEQUENCE: 8

Glu Val Gln Leu Leu 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 Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Asn Ser Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn 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 Asp Asn Tyr Tyr Tyr Tyr Met Asp Val Trp Gly Lys Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

<210> SEQ ID NO 9
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23A8 HCDR1

<400> SEQUENCE: 9

Gly Phe Thr Phe Ser Ser Ser Ala Met His
1 5 10

<210> SEQ ID NO 10
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23A8 HCDR2

<400> SEQUENCE: 10

Gly Ile Ser Gly Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

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Gly

<210> SEQ ID NO 11
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23A8 HCDR3

<400> SEQUENCE: 11

Asp Asn Asn Tyr Tyr Tyr Tyr Met Asp Val
1 5 10

<210> SEQ ID NO 12
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23A8 VH

<400> SEQUENCE: 12

Glu Val Gln Leu Leu 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 Ser Ser Ser
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Gly Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn 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 Asp Asn Asn Tyr Tyr Tyr Tyr Met Asp Val Trp Gly Lys Gly
100 105 110

Thr Thr Val Thr Val Ser Ser
115

<210> SEQ ID NO 13
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23A11 HCDR1

<400> SEQUENCE: 13

Gly Tyr Thr Phe Thr Asp Tyr Ser Leu His
1 5 10

<210> SEQ ID NO 14
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23A11 HCDR2

<400> SEQUENCE: 14

Glu Val Ile Pro Met Phe Asp Thr Ala Tyr Tyr Ala Gln Thr Phe Gln
1 5 10 15

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Gly

<210> SEQ ID NO 15
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23A11 HCDR3

<400> SEQUENCE: 15

Glu Pro Phe Thr Met Val Arg Gly Gly Arg Tyr Tyr Tyr Tyr Gly Met
1 5 10 15

Asp Val

<210> SEQ ID NO 16
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23A11 VH

<400> SEQUENCE: 16

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Ser Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Glu Val Ile Pro Met Phe Asp Thr Ala Tyr Tyr Ala Gln Thr Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Pro Phe Thr Met Val Arg Gly Gly Arg Tyr Tyr Tyr Tyr
100 105 110

Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 17
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23H9 HCDR1

<400> SEQUENCE: 17

Gly Gly Thr Phe Ser Ser Ser Val Ile Ser
1 5 10

<210> SEQ ID NO 18
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23H9 HCDR2

<400> SEQUENCE: 18

Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

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Gly

<210> SEQ ID NO 19
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23H9 HCDR3

<400> SEQUENCE: 19

Glu Gly Leu Gly Cys Ser Gly Gly Ser Cys Tyr Ser Gly Tyr Tyr Tyr
1 5 10 15

Gly Met Asp Val
20

<210> SEQ ID NO 20
<211> LENGTH: 129
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23H9 VH

<400> SEQUENCE: 20

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Ser
20 25 30

Val Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Leu Gly Cys Ser Gly Gly Ser Cys Tyr Ser Gly Tyr
100 105 110

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> SEQ ID NO 21
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 24H9 HCDR1

<400> SEQUENCE: 21

Gly Phe Thr Phe Ser Ser Tyr Trp Met Ser
1 5 10

<210> SEQ ID NO 22
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 24H9 HCDR2

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<400> SEQUENCE: 22

Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 23
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 24H9 HCDR3

<400> SEQUENCE: 23

Ser Pro Leu Gln Trp Val Asp Val
1 5

<210> SEQ ID NO 24
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 24H9 VH

<400> SEQUENCE: 24

Glu Val Gln Leu Leu 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 Ser Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn 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 Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 25
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19B6 LCDR1

<400> SEQUENCE: 25

Arg Ala Ser Gln Ser Ile Asn Ser Trp Leu Ala
1 5 10

<210> SEQ ID NO 26
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19B6 LCDR2

<400> SEQUENCE: 26

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Tyr Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 27
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19B6 LCDR3

<400> SEQUENCE: 27

Gln Gln Gly Tyr Ser Val Pro Leu Ser
1 5

<210> SEQ ID NO 28
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19B6 VL

<400> SEQUENCE: 28

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 Ser Ile Asn Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Ala Ser Ser Leu Gln Ser 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 Gly Tyr Ser Val Pro Leu
85 90 95

Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> SEQ ID NO 29
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19B10 LCDR1

<400> SEQUENCE: 29

Arg Ala Ser Gln Ser Val Ser Thr Trp Leu Ala
1 5 10

<210> SEQ ID NO 30
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19B10 LCDR2

<400> SEQUENCE: 30

Ala Ala Ser Asn Leu Glu Thr
1 5

<210> SEQ ID NO 31

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<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19B10 LCDR3

<400> SEQUENCE: 31

Gln Gln Thr Tyr Ser Thr Pro Tyr Thr
1 5

<210> SEQ ID NO 32
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 19B10 VL

<400> SEQUENCE: 32

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 Ser Val Ser Thr Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Asn Leu Glu 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 Thr Tyr Ser Thr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> SEQ ID NO 33
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23A8 LCDR1

<400> SEQUENCE: 33

Arg Ala Ser Gln Ser Ile Gly Thr Trp Leu Ala
1 5 10

<210> SEQ ID NO 34
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23A8 LCDR2

<400> SEQUENCE: 34

Ala Ala Ser Thr Leu Arg Ser
1 5

<210> SEQ ID NO 35
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23A8 LCDR3

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<400> SEQUENCE: 35

Gln Gln Ser Tyr Ser Thr Pro Tyr Thr
1 5

<210> SEQ ID NO 36
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23A8 VL

<400> SEQUENCE: 36

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 Ser Ile Gly Thr Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Arg Ser 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 Ser Tyr Ser Thr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> SEQ ID NO 37
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23A11 LCDR1

<400> SEQUENCE: 37

Arg Ala Ser Gln Asn Ile Asn Lys Asn Leu Asn
1 5 10

<210> SEQ ID NO 38
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23A11 LCDR2/39H11 LCDR2

<400> SEQUENCE: 38

Asp Ala Ser Asn Leu Gln Ser
1 5

<210> SEQ ID NO 39
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23A11 LCDR3

<400> SEQUENCE: 39

Gln His Ser Glu Thr
1 5

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<210> SEQ ID NO 40
<211> LENGTH: 103
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23A11 VL

<400> SEQUENCE: 40

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 Asn Ile Asn Lys Asn
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Leu Gln Ser 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 His Ser Glu Thr Phe Gly Gln
85 90 95

Gly Thr Lys Val Glu Ile Lys
100

<210> SEQ ID NO 41
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23H9 LCDR1/31B1 LCDR1/33C4 LCDR1/33G8 LCDR1

<400> SEQUENCE: 41

Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp
1 5 10 15

<210> SEQ ID NO 42
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23H9 LCDR2

<400> SEQUENCE: 42

Leu Ser Ser His Arg Ala Ser
1 5

<210> SEQ ID NO 43
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23H9 LCDR3

<400> SEQUENCE: 43

Met Gln Gly Ala His Trp Pro Tyr Thr
1 5

<210> SEQ ID NO 44
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23H9 VL

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<400> SEQUENCE: 44

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35 40 45

Pro Gln Leu Leu Ile Tyr Leu Ser Ser His Arg Ala Ser Gly Val Pro
    50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                85 90 95

Ala His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100 105 110

<210> SEQ ID NO 45
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 24H9 LCDR1

<400> SEQUENCE: 45

Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala
1 5 10

<210> SEQ ID NO 46
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 24H9 LCDR2

<400> SEQUENCE: 46

Ser Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 47
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 24H9 LCDR3/32G6 LCDR3/38A4 LCDR3/38A6 LCDR3/
      38A8 LCDR3/38C11 LCDR3/38G11 LCDR3/38G9 LCDR3/39B11 LCDR3/39B3
      LCDR3/39B6 LCDR3/39F11 LCDR3/39G5 LCDR3/39H2 LCDR3

<400> SEQUENCE: 47

Gln Gln Ala Asn Ser Phe Pro Phe Thr
1 5

<210> SEQ ID NO 48
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 24H9 VL

<400> SEQUENCE: 48

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 Gly Ile Ser Ser Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ser Ala Ser Ser Leu Gln Ser 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 Ala Asn Ser Phe Pro Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105


<210> SEQ ID NO 49
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 31B1 LCDR2

<400> SEQUENCE: 49

Glu Ala Ser Ser Leu His Ser
1               5


<210> SEQ ID NO 50
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 31B1 LCDR3

<400> SEQUENCE: 50

Met Gln Gly Thr His Trp Pro Tyr Thr
1               5


<210> SEQ ID NO 51
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 31B1 VL

<400> SEQUENCE: 51

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

Pro Gln Leu Leu Ile Tyr Glu Ala Ser Ser Leu His Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                85                  90                  95

Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
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<210> SEQ ID NO 52
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 33C4 LCDR2

<400> SEQUENCE: 52

Glu Ala Ser Ser Leu His Thr
1 5

<210> SEQ ID NO 53
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 33C4 LCDR3

<400> SEQUENCE: 53

Met Gln Gly Ser His Trp Pro Tyr Thr
1 5

<210> SEQ ID NO 54
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 33C4 VL

<400> SEQUENCE: 54

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Glu Ala Ser Ser Leu His Thr Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
85 90 95

Ser His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> SEQ ID NO 55
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 33G8 LCDR2

<400> SEQUENCE: 55

Gln Ala Ser Thr Leu Gly Ser
1 5

<210> SEQ ID NO 56
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: 33G8 LCDR3

<400> SEQUENCE: 56

Met Gln Gly Thr His Trp Pro Tyr Thr
1 5

<210> SEQ ID NO 57
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 33G8 VL

<400> SEQUENCE: 57

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Gln Ala Ser Thr Leu Gly Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
85 90 95

Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> SEQ ID NO 58
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 34C1 LCDR1

<400> SEQUENCE: 58

Arg Ser Ser Glu Ser Leu Leu Tyr Ser Asn Gly Asn Thr Tyr Leu Asp
1 5 10 15

<210> SEQ ID NO 59
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 34C1 LCDR2

<400> SEQUENCE: 59

Glu Val Ser Asn Arg Ala Ser
1 5

<210> SEQ ID NO 60
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 34C1 LCDR3

<400> SEQUENCE: 60

Met Gln Gly Thr Arg Trp Pro Tyr Thr

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1 5

<210> SEQ ID NO 61
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 34C1 VL

<400> SEQUENCE: 61

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Glu Ser Leu Leu Tyr Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Glu Val Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
85 90 95

Thr Arg Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> SEQ ID NO 62
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23H9 derivatives motif LCDR1
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: X can be Q or E
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: X can be H or Y
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: X can be Y or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: X can be T or N

<400> SEQUENCE: 62

Arg Ser Ser Xaa Ser Leu Leu Xaa Ser Asn Gly Xaa Xaa Tyr Leu Asp
1 5 10 15

<210> SEQ ID NO 63
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23H9 derivatives motif LCDR2
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: X can be L, Q or E
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)

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<223> OTHER INFORMATION: X can be S, A, or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: X can be H, N, T, or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: X can be R or L
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: X can be G, A, or H
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: X can be S or T

<400> SEQUENCE: 63

Xaa Xaa Ser Xaa Xaa Xaa Xaa
1 5

<210> SEQ ID NO 64
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23H9 derivatives motif LCDR3
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: X can be A, T, or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: X can be H or R

<400> SEQUENCE: 64

Met Gln Gly Xaa Xaa Trp Pro Tyr Thr
1 5

<210> SEQ ID NO 65
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 23H9 derivatives motif VL
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (27)..(27)
<223> OTHER INFORMATION: X can be Q or E
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: X can be H or Y
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (35)..(35)
<223> OTHER INFORMATION: X can be Y or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (36)..(36)
<223> OTHER INFORMATION: X can be T or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (55)..(55)
<223> OTHER INFORMATION: X can be L, Q or E
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (56)..(56)
<223> OTHER INFORMATION: X can be S, A, or V
<220> FEATURE:

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<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (58)..(58)
<223> OTHER INFORMATION: X can be H, N, T, or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (59)..(59)
<223> OTHER INFORMATION: X can be R or L
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (60)..(60)
<223> OTHER INFORMATION: X can be G, A, or H
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (61)..(61)
<223> OTHER INFORMATION: X can be S or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (97)..(97)
<223> OTHER INFORMATION: X can be A, T, or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (98)..(98)
<223> OTHER INFORMATION: X can be H or R

<400> SEQUENCE: 65

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Xaa Ser Leu Leu Xaa Ser
20 25 30

Asn Gly Xaa Xaa Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Xaa Xaa Ser Xaa Xaa Xaa Xaa Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
85 90 95

Xaa Xaa Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> SEQ ID NO 66
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 32A11 LCDR1/38A8 LCDR1

<400> SEQUENCE: 66

Arg Ala Ser Glu Ser Ile Ser Ile Trp Leu Ala
1 5 10

<210> SEQ ID NO 67
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 32A11 LCDR2/32D11 LCDR2/38A8 LCDR2/39B3 LCDR2

<400> SEQUENCE: 67

Asp Ala Ser Asn Leu Glu Thr
1 5

<210> SEQ ID NO 68
<211> LENGTH: 9

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 32A11 LCDR3/39H11 LCDR3

<400> SEQUENCE: 68

Gln Gln Ala Asp Ser Phe Pro Phe Thr
1 5

<210> SEQ ID NO 69
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 32A11 VL

<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 Arg Ala Ser Glu Ser Ile Ser Ile Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asn Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asp Ser Phe Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> SEQ ID NO 70
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 32D11 LCDR1

<400> SEQUENCE: 70

Arg Ala Ser Gln Ser Ile Asn Ile Trp Leu Ala
1 5 10

<210> SEQ ID NO 71
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 32D11 LCDR3/38B10 LCDR3

<400> SEQUENCE: 71

Gln Gln Gly Tyr Ser Phe Pro Phe Thr
1 5

<210> SEQ ID NO 72
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 32D11 VL

<400> SEQUENCE: 72

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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 Ser Ile Asn Ile Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Asn Leu Glu 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 Gly Tyr Ser Phe Pro Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105


<210> SEQ ID NO 73
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 32D2 LCDR1

<400> SEQUENCE: 73

Arg Ala Ser Gln Gly Ile Ser Arg Trp Leu Ala
1               5                   10


<210> SEQ ID NO 74
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 32D2 LCDR2

<400> SEQUENCE: 74

Glu Ala Ser Thr Leu Gln Ser
1               5


<210> SEQ ID NO 75
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 32D2 LCDR3/38B1 LCDR3/38H3 LCDR3/39G8 LCDR3/
      39H7 LCDR3

<400> SEQUENCE: 75

Gln Gln Ala Tyr Ser Phe Pro Phe Thr
1               5


<210> SEQ ID NO 76
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 32D2 VL

<400> SEQUENCE: 76

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 Gly Ile Ser Arg Trp
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            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Glu Ala Ser Thr Leu Gln Ser 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 Ala Tyr Ser Phe Pro Phe
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
            100                 105


<210> SEQ ID NO 77
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 32G6 LCDR1/38A11 LCDR1/38A4 LCDR1/39A3 LCDR1/
      39B11 LCDR1

<400> SEQUENCE: 77

Arg Ala Ser Gln Ser Ile Ser Ser Trp Leu Ala
1               5                   10


<210> SEQ ID NO 78
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 32G6 LCDR2/ 38A11 LCDR2/39F11 LCDR2

<400> SEQUENCE: 78

Asp Ala Ser Thr Leu Gln Ser
1               5


<210> SEQ ID NO 79
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 32G6 VL

<400> SEQUENCE: 79

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 Ser Ile Ser Ser Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Thr Leu Gln Ser 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 Ala Asn Ser Phe Pro Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105
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<210> SEQ ID NO 80
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38A10 LCDR1/38B1 LCDR1/38B10 LCDR1 /39F11 LCDR1

<400> SEQUENCE: 80

Arg Ala Ser Gln Ser Ile Ser Thr Trp Leu Ala
1 5 10

<210> SEQ ID NO 81
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38A10 LCDR2

<400> SEQUENCE: 81

Asp Ala Ser Arg Leu Gln Asn
1 5

<210> SEQ ID NO 82
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38A10 LCDR3/38B2 LCDR3

<400> SEQUENCE: 82

Gln Gln Gly Asp Ser Phe Pro Phe Thr
1 5

<210> SEQ ID NO 83
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38A10 VL

<400> SEQUENCE: 83

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 Ser Ile Ser Thr Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Arg Leu Gln Asn 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 Gly Asp Ser Phe Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> SEQ ID NO 84
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38A11 LCDR3

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<400> SEQUENCE: 84

Gln Gln Gly Asn Ser Phe Pro Phe Thr
1 5

<210> SEQ ID NO 85
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38A11 VL

<400> SEQUENCE: 85

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 Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Thr Leu Gln Ser 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 Gly Asn Ser Phe Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> SEQ ID NO 86
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38A4 LCDR2

<400> SEQUENCE: 86

Asp Ala Ser Asn Leu Gln Thr
1 5

<210> SEQ ID NO 87
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38A4 VL

<400> SEQUENCE: 87

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 Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Leu Gln 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 Ala Asn Ser Phe Pro Phe

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                85                  90                  95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100                 105


<210> SEQ ID NO 88
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38A6 LCDR1

<400> SEQUENCE: 88

Arg Ala Ser Gln Asp Ile Ser Arg Trp Leu Gly
1               5                   10


<210> SEQ ID NO 89
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38A6 LCDR2

<400> SEQUENCE: 89

Ala Ala Ser Thr Leu Gln Ser
1               5


<210> SEQ ID NO 90
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38A6 VL

<400> SEQUENCE: 90

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 Ile Ser Arg Trp
            20                  25                  30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Thr Leu Gln Ser 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 Ala Asn Ser Phe Pro Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210> SEQ ID NO 91
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38A8 VL

<400> SEQUENCE: 91

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 Glu Ser Ile Ser Ile Trp
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            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Asn Leu Glu 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 Ala Asn Ser Phe Pro Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105


<210> SEQ ID NO 92
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38B1 LCDR2

<400> SEQUENCE: 92

Glu Ala Ser Lys Leu Glu Arg
1               5


<210> SEQ ID NO 93
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38B1 VL

<400> SEQUENCE: 93

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 Ser Ile Ser Thr Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Glu Ala Ser Lys Leu Glu Arg 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 Ala Tyr Ser Phe Pro Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105


<210> SEQ ID NO 94
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38B10 LCDR2

<400> SEQUENCE: 94

Asp Ala Ser Thr Leu Gln Thr
1               5


<210> SEQ ID NO 95
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<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38B10 VL

<400> SEQUENCE: 95

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 Ser Ile Ser Thr Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Ser Asp Ala Ser Thr Leu Gln 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 Gly Tyr Ser Phe Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> SEQ ID NO 96
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38B2 LCDR1

<400> SEQUENCE: 96

Arg Ala Ser Glu Ser Ile Ser Ser Trp Leu Ala
1 5 10

<210> SEQ ID NO 97
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38B2 LCDR2

<400> SEQUENCE: 97

Asp Ala Ser Ser Leu Glu Ser
1 5

<210> SEQ ID NO 98
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38B2 VL

<400> SEQUENCE: 98

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 Glu Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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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 Gly Asp Ser Phe Pro Phe
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210> SEQ ID NO 99
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38C11 LCDR1

<400> SEQUENCE: 99

Arg Ala Ser Gln Ser Ile Ser Arg Trp Leu Ala
1               5                   10


<210> SEQ ID NO 100
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38C11 LCDR2

<400> SEQUENCE: 100

Asp Ala Ser Thr Val Gln Ser
1               5


<210> SEQ ID NO 101
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38C11 VL

<400> SEQUENCE: 101

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 Ser Ile Ser Arg Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Ser Asp Ala Ser Thr Val Gln Ser 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 Ala Asn Ser Phe Pro Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105


<210> SEQ ID NO 102
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38C6 LCDR1

<400> SEQUENCE: 102
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Arg Ala Gly Arg Asp Ile Asn Lys Trp Val Ala
1               5                   10


<210> SEQ ID NO 103
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38C6 LCDR2/38G11 LCDR2/38G9 LCDR2/39A3 LCDR2/
      39G5 LCDR2

<400> SEQUENCE: 103

Asp Ala Ser Ser Leu Gln Ser
1               5


<210> SEQ ID NO 104
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38C6 LCDR3

<400> SEQUENCE: 104

Gln Gln Ala Asn Ser Phe Pro Phe Ala
1               5


<210> SEQ ID NO 105
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38C6 VL

<400> SEQUENCE: 105

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 Gly Arg Asp Ile Asn Lys Trp
            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Ser Leu Gln Ser 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 Ala Asn Ser Phe Pro Phe
                85                  90                  95

Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 106
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38G11 LCDR1

<400> SEQUENCE: 106

Arg Ala Ser Glu Asn Ile Ser Arg Trp Leu Ala
1               5                   10
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<210> SEQ ID NO 107
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38G11 VL

<400> SEQUENCE: 107

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 Glu Asn Ile Ser Arg Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Gln Ser 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 Ala Asn Ser Phe Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> SEQ ID NO 108
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38G9 LCDR1

<400> SEQUENCE: 108

Arg Val Ser Gln Ser Ile Ser Asn Trp Leu Ala
1 5 10

<210> SEQ ID NO 109
<211> LENGTH: 97
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38G9 VL

<400> SEQUENCE: 109

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 Val Ser Gln Ser Ile Ser Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Gln Ser 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 Ala Asn Ser Phe Pro Phe
85 90 95

Thr

<210> SEQ ID NO 110
<211> LENGTH: 11

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38H3 LCDR1

<400> SEQUENCE: 110

Arg Ala Ser Gln Gly Ile Ser Thr Trp Leu Ala
1 5 10

<210> SEQ ID NO 111
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38H3 LCDR2/39B11 LCDR2

<400> SEQUENCE: 111

Glu Ala Ser Arg Leu Gln Ser
1 5

<210> SEQ ID NO 112
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38H3 VL

<400> SEQUENCE: 112

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 Gly Ile Ser Thr Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Glu Ala Ser Arg Leu Gln Ser 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 Ala Tyr Ser Phe Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> SEQ ID NO 113
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39A3 LCDR3

<400> SEQUENCE: 113

Gln Gln Gly Asp Ser Phe Pro Leu Thr
1 5

<210> SEQ ID NO 114
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39A3 VL

<400> SEQUENCE: 114

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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 Ser Ile Ser Ser Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Ser Leu Gln Ser 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 Gly Asp Ser Phe Pro Leu
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 115
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39B11 VL

<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 Arg Ala Ser Gln Ser Ile Ser Ser Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Glu Ala Ser Arg Leu Gln Ser 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 Ala Asn Ser Phe Pro Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105


<210> SEQ ID NO 116
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39B3 LCDR1

<400> SEQUENCE: 116

Arg Ala Ser Gln Ser Ile Gly Pro Trp Leu Ala
1               5                   10


<210> SEQ ID NO 117
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39B3 VL

<400> SEQUENCE: 117
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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 Ser Ile Gly Pro Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Asn Leu Glu 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 Ala Asn Ser Phe Pro Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105


<210> SEQ ID NO 118
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39B6 LCDR1

<400> SEQUENCE: 118

Arg Ala Ser Glu Asp Ile Ser His Trp Leu Ala
1               5                   10


<210> SEQ ID NO 119
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39B6 LCDR2

<400> SEQUENCE: 119

Asp Ala Lys Asp Leu His Pro
1               5


<210> SEQ ID NO 120
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39B6 VL

<400> SEQUENCE: 120

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 Glu Asp Ile Ser His Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Lys Asp Leu His Pro 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 Ala Asn Ser Phe Pro Phe
                85                  90                  95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
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100 105

<210> SEQ ID NO 121
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39F11 VL

<400> SEQUENCE: 121

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 Ser Ile Ser Thr Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Thr Leu Gln Ser 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 Ala Asn Ser Phe Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> SEQ ID NO 122
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39G5 LCDR1

<400> SEQUENCE: 122

Arg Ala Ser Gln Asn Ile Asn Val Trp Leu Ala
1 5 10

<210> SEQ ID NO 123
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39G5 VL

<400> SEQUENCE: 123

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 Asn Ile Asn Val Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Gln Ser 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 Ala Asn Ser Phe Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

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<210> SEQ ID NO 124
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39G8 LCDR1

<400> SEQUENCE: 124

Arg Ala Ser Gln Gly Ile Ser Pro Trp Leu Ala
1 5 10

<210> SEQ ID NO 125
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39G8 LCDR2

<400> SEQUENCE: 125

Asp Ala Ser Lys Leu Glu Thr
1 5

<210> SEQ ID NO 126
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39G8 VL

<400> SEQUENCE: 126

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 Gly Ile Ser Pro Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Lys Leu Glu 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 Ala Tyr Ser Phe Pro Phe
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 127
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39H11 LCDR1

<400> SEQUENCE: 127

Arg Ala Ser Gln Ser Ile Gly Ile Trp Val Ala
1 5 10

<210> SEQ ID NO 128
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: 39H11 VL

<400> SEQUENCE: 128

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 Ser Ile Gly Ile Trp
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Leu Gln Ser 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 Ala Asp Ser Phe Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 129
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39H2 LCDR1

<400> SEQUENCE: 129

Arg Ala Ser Gln Asn Ile Gly Pro Trp Leu Ala
1 5 10

<210> SEQ ID NO 130
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39H2 LCDR2

<400> SEQUENCE: 130

Asp Ala Ser Thr Leu His Ser
1 5

<210> SEQ ID NO 131
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39H2 VL

<400> SEQUENCE: 131

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 Asn Ile Gly Pro Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Thr Leu His Ser 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

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Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Phe
                85                  90                  95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100                 105


<210> SEQ ID NO 132
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39H7 LCDR1

<400> SEQUENCE: 132

Arg Ala Ser Gln Ser Ile Ser Asn Trp Leu Ala
1               5                   10


<210> SEQ ID NO 133
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39H7 LCDR2

<400> SEQUENCE: 133

Asp Ala Ser Asn Leu Gln Ala
1               5


<210> SEQ ID NO 134
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 39H7 VL

<400> SEQUENCE: 134

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 Ser Ile Ser Asn Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Asn Leu Gln Ala 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 Ala Tyr Ser Phe Pro Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105


<210> SEQ ID NO 135
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 24H9 derivatives motif LCR1
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: X can be A or V
<220> FEATURE:
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<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: X can be S or G
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: X can be Q, E, or R
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: X can be G, S, D or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: X can be G, S, or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: X can be S, I, R, T, K, P, N, H, or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: X can be L or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: X can be G or A

<400> SEQUENCE: 135

Arg Xaa Xaa Xaa Xaa Ile Xaa Xaa Trp Xaa Xaa
1 5 10

<210> SEQ ID NO 136
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 24H9 derivatives motif LCR2
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: X can be S, D, E, or A
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: X can be S, or K
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: X can be S, N, T, R, or D
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: X can be L or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: X can be Q, E, or H
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: X can be S, N, A, R, P, or T

<400> SEQUENCE: 136

Xaa Ala Xaa Xaa Xaa Xaa Xaa
1 5

<210> SEQ ID NO 137
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: 24H9 derivatives motif LCR3
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: X can be A, or G
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: X can be N, D, or Y
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: X can be F or L
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: X can be A, or T

<400> SEQUENCE: 137

Gln Gln Xaa Xaa Ser Phe Pro Xaa Xaa
1   5

<210> SEQ ID NO 138
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 24H9 derivatives motif VL
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (25)..(25)
<223> OTHER INFORMATION: X can be A or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (26)..(26)
<223> OTHER INFORMATION: X can be S or G
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (27)..(27)
<223> OTHER INFORMATION: X can be Q, E, or R
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (28)..(28)
<223> OTHER INFORMATION: X can be G, S, D or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: X can be G, S, or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: X can be S, I, R, T, K, P, N,H, or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (33)..(33)
<223> OTHER INFORMATION: X can be L or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: X can be G or A
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (50)..(50)
<223> OTHER INFORMATION: X can be S, D, E, or A
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (52)..(52)
<223> OTHER INFORMATION: X can be S, or K
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (53)..(53)
<223> OTHER INFORMATION: X can be S, N, T, R, or D
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE

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<222> LOCATION: (54)..(54)
<223> OTHER INFORMATION: X can be L or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (55)..(55)
<223> OTHER INFORMATION: X can be Q, E, or H
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (56)..(56)
<223> OTHER INFORMATION: X can be S, N, A, R, P, or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (91)..(91)
<223> OTHER INFORMATION: X can be A, or G
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (92)..(92)
<223> OTHER INFORMATION: X can be N, D, or Y
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (96)..(96)
<223> OTHER INFORMATION: X can be F or L
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (97)..(97)
<223> OTHER INFORMATION: X can be A, or T

<400> SEQUENCE: 138

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 Xaa Xaa Xaa Xaa Ile Xaa Xaa Trp
20 25 30

Xaa Xaa Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Xaa Ala Xaa Xaa Xaa Xaa Xaa 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 Xaa Xaa Ser Phe Pro Xaa
85 90 95

Xaa Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> SEQ ID NO 139
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: R3A9 HCDR1

<400> SEQUENCE: 139

Gly His Thr Phe Thr Ser Tyr Tyr Ile His
1 5 10

<210> SEQ ID NO 140
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: R3A9 HCDR2

<400> SEQUENCE: 140

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
1 5 10 15

-continued

Gln Gly

<210> SEQ ID NO 141
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: R3A9 HCDR3

<400> SEQUENCE: 141

Asp Arg Ala Tyr Gly Gly Ala Gly Asp Tyr
1 5 10

<210> SEQ ID NO 142
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: R3A9 VH

<400> SEQUENCE: 142

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly His Thr Phe Thr Ser Tyr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Ala Tyr Gly Gly Ala Gly Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 143
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: R3A9 LCDR1

<400> SEQUENCE: 143

Arg Ala Ser Gln Ser Val Gly Thr Trp Leu Ala
1 5 10

<210> SEQ ID NO 144
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: R3A9 LCDR2

<400> SEQUENCE: 144

Ser Ala Ser Thr Leu Gln Ser
1 5

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<210> SEQ ID NO 145
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: R3A9 LCDR3

<400> SEQUENCE: 145

Gln Gln Ser Tyr Ser Ala Pro Leu Thr
1 5

<210> SEQ ID NO 146
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: R3A9 VL

<400> SEQUENCE: 146

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 Ser Val Gly Thr Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Thr Leu Gln Ser 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 Ser Tyr Ser Ala Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 147
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m3A7 LCDR1

<400> SEQUENCE: 147

Arg Ala Ser Arg Ser Ile Ser Asn Trp Leu Ala
1 5 10

<210> SEQ ID NO 148
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m3A7 LCDR2/m2C1 LCDR2

<400> SEQUENCE: 148

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 149
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m3A7 LCDR3

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<400> SEQUENCE: 149

Gln Gln Ser Tyr Ser Ala Pro Val Thr
1 5

<210> SEQ ID NO 150
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m3A7 VL

<400> SEQUENCE: 150

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 Arg Ser Ile Ser Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser 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 Ser Tyr Ser Ala Pro Val
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 151
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m2C1 LCDR1

<400> SEQUENCE: 151

Arg Ala Ser Arg Ser Ile Ser Ser Trp Leu Ala
1 5 10

<210> SEQ ID NO 152
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m2C1 LCDR3

<400> SEQUENCE: 152

Gln Gln Ser Tyr Ser Ile Pro Ala Thr
1 5

<210> SEQ ID NO 153
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m2C1 VL

<400> SEQUENCE: 153

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Ser Ile Ser Ser Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser 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 Ser Tyr Ser Ile Pro Ala
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 154
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m2A1 LCDR1

<400> SEQUENCE: 154

Arg Ala Ser Arg Gly Ile Ser Ser Trp Leu Ala
1               5                   10


<210> SEQ ID NO 155
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m2A1 LCDR3

<400> SEQUENCE: 155

Gln Gln Ser Tyr Ser Pro Pro Trp Thr
1               5


<210> SEQ ID NO 156
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m2A1 VL

<400> SEQUENCE: 156

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 Arg Gly Ile Ser Ser Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser 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 Ser Tyr Ser Pro Pro Trp
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
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<210> SEQ ID NO 157
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m4A5 LCDR1/m3C6 LCDR1

<400> SEQUENCE: 157

Arg Ala Ser Gln Ser Ile Asp Thr Trp Leu Ala
1 5 10

<210> SEQ ID NO 158
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m4A5 LCDR2

<400> SEQUENCE: 158

Ala Ala Ser Thr Leu Glu Ser
1 5

<210> SEQ ID NO 159
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m4A5 LCDR3

<400> SEQUENCE: 159

Gln Gln Ser Tyr Arg Ala Pro Leu Thr
1 5

<210> SEQ ID NO 160
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m4A5 VL

<400> SEQUENCE: 160

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 Ser Ile Asp Thr Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Glu Ser 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 Ser Tyr Arg Ala Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 161
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m4D1 LCDR1

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<400> SEQUENCE: 161

Arg Ala Ser Gln Ser Ile Ser Ala Trp Leu Ala
1 5 10

<210> SEQ ID NO 162
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m4D1 LCDR2

<400> SEQUENCE: 162

Lys Ala Ser Ser Leu Glu Ser
1 5

<210> SEQ ID NO 163
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m4D1 LCDR3

<400> SEQUENCE: 163

Gln Gln Ser Tyr Ser Pro Pro Ala Thr
1 5

<210> SEQ ID NO 164
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m4D1 VL

<400> SEQUENCE: 164

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 Ser Ile Ser Ala Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Ser Leu Glu Ser 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 Ser Tyr Ser Pro Pro Ala
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 165
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m3C6 LCDR2

<400> SEQUENCE: 165

Glu Ala Ser Ser Leu Gln Gly
1 5

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<210> SEQ ID NO 166
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m3C6 LCDR3

<400> SEQUENCE: 166

Gln Gln Ser Tyr Ser Thr Trp Thr
1 5

<210> SEQ ID NO 167
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m3C6 VL

<400> SEQUENCE: 167

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 Ser Ile Asp Thr Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Glu Ala Ser Ser Leu Gln Gly 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 Ser Tyr Ser Thr Trp Thr
85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 168
<211> LENGTH: 447
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38B2 full length HC

<400> SEQUENCE: 168

Glu Val Gln Leu Leu 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 Ser Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn 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 Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu

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        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 169
<211> LENGTH: 447
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38B2 HC (T350V/T366L/ K392L/ T394W) LALAPG

<400> SEQUENCE: 169

Glu Val Gln Leu Leu 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 Ser Ser Tyr
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           20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
       35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn 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 Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr Thr
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro
            340                 345                 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430
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His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> SEQ ID NO 170
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38B2 full length LC

<400> SEQUENCE: 170

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 Glu Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu Ser 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 Gly Asp Ser Phe Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu 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 171
<211> LENGTH: 449
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m3A7 full length mHC LALAPG

<400> SEQUENCE: 171

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly His Thr Phe Thr Ser Tyr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe

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    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Arg Ala Tyr Gly Gly Ala Gly Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr
        115                 120                 125

Pro Leu Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu
    130                 135                 140

Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp
145                 150                 155                 160

Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser
            180                 185                 190

Thr Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser
        195                 200                 205

Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys
    210                 215                 220

Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Ala Ala Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser
                245                 250                 255

Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp
            260                 265                 270

Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr
        275                 280                 285

Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val
    290                 295                 300

Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu
305                 310                 315                 320

Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Gly Ala Pro Ile Glu Arg
                325                 330                 335

Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val
            340                 345                 350

Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr
        355                 360                 365

Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr
    370                 375                 380

Asn Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys
                405                 410                 415

Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu
            420                 425                 430

Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly
        435                 440                 445

Lys
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<210> SEQ ID NO 172
<211> LENGTH: 449
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m3A7 mHC (L351Y/F405A/Y407V) LALAPG

<400> SEQUENCE: 172

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly His Thr Phe Thr Ser Tyr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Ala Tyr Gly Gly Ala Gly Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr
115 120 125

Pro Leu Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu
130 135 140

Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp
145 150 155 160

Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser
180 185 190

Thr Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser
195 200 205

Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys
210 215 220

Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser
245 250 255

Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp
260 265 270

Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr
275 280 285

Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val
290 295 300

Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu
305 310 315 320

Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Gly Ala Pro Ile Glu Arg
325 330 335

Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val
340 345 350

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```
Tyr Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr
        355                 360                 365

Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr
    370                 375                 380

Asn Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Tyr Ala Met Val Ser Lys Leu Arg Val Glu Lys
                405                 410                 415

Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu
            420                 425                 430

Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly
        435                 440                 445

Lys
```

<210> SEQ ID NO 173
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m3A7 full length mLC

<400> SEQUENCE: 173

```
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 Arg Ser Ile Ser Asn Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser 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 Ser Tyr Ser Ala Pro Val
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Ala Asp Ala Ala
            100                 105                 110

Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125

Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140

Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145                 150                 155                 160

Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175

Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190

Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205

Phe Asn Arg Asn Glu Cys
    210
```

<210> SEQ ID NO 174
<211> LENGTH: 688
<212> TYPE: PRT

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hSD15 + 38B2 HC LALAPG

<400> SEQUENCE: 174

```
Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                  10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
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    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            580                 585                 590

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        595                 600                 605

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 175
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hSD15 + 38B2HC (T350V/L351Y/F405A/Y407V) LALAPG

<400> SEQUENCE: 175

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
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        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445
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```
Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
            580                 585                 590

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        595                 600                 605

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 176
<211> LENGTH: 656
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38B2HC LALAPG + hSD15

<400> SEQUENCE: 176

Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn 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 Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr Thr
            100                 105                 110
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```
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ser Cys
        435                 440                 445

Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser Tyr
    450                 455                 460

Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys Arg
465                 470                 475                 480

Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala Thr
                485                 490                 495

Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp Pro
            500                 505                 510
```

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```
Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly Ser Gly Gly
        515                 520                 525

Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Gln Asn Trp
    530                 535                 540

Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser
545                 550                 555                 560

Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser
                565                 570                 575

Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile
            580                 585                 590

Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu
        595                 600                 605

Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu
    610                 615                 620

Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu
625                 630                 635                 640

Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser
                645                 650                 655


<210> SEQ ID NO 177
<211> LENGTH: 656
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38B2 HC (T350V/L351Y/F405A/Y407V) LALAPG +
      hSD15

<400> SEQUENCE: 177

Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn 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 Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr Thr
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205
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```
Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro
            340                 345                 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ser Cys
        435                 440                 445

Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser Tyr
    450                 455                 460

Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys Arg
465                 470                 475                 480

Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala Thr
                485                 490                 495

Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp Pro
            500                 505                 510

Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly Ser Gly Gly
        515                 520                 525

Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Gln Asn Trp
    530                 535                 540

Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser
545                 550                 555                 560

Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser
                565                 570                 575

Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile
            580                 585                 590

Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu
        595                 600                 605
```

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```
Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu
    610                 615                 620

Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu
625                 630                 635                 640

Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser
                645                 650                 655


<210> SEQ ID NO 178
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: N65A_hSD15+38B2 HC (T350V/L351Y/F405A/Y407V)
      LALAPG

<400> SEQUENCE: 178

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Ala Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300
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Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
            580                 585                 590

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        595                 600                 605

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685
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<210> SEQ ID NO 179
<211> LENGTH: 688

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: N65D_hSD15 + 38B2 HC (T350V/L351Y/F405A/Y407V)
LALAPG

<400> SEQUENCE: 179

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1 5 10 15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
20 25 30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
35 40 45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
50 55 60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65 70 75 80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
85 90 95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
100 105 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
115 120 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
130 135 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145 150 155 160

Glu Asp Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
165 170 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
180 185 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
195 200 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
210 215 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225 230 235 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
245 250 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
260 265 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
275 280 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
290 295 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305 310 315 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
325 330 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
340 345 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
355 360 365

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Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
            580                 585                 590

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        595                 600                 605

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 180
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: N65S_hSD15+38B2 HC (T350V/L351Y/F405A/Y407V)

<400> SEQUENCE: 180

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30
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Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Ser Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430
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Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
            580                 585                 590

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        595                 600                 605

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 181
<211> LENGTH: 690
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mSD15 + m3A7 mHc LALAPG

<400> SEQUENCE: 181

Ile Thr Cys Pro Pro Pro Val Ser Ile Glu His Ala Asp Ile Arg Val
1               5                   10                  15

Lys Asn Tyr Ser Val Asn Ser Arg Glu Arg Tyr Val Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Thr Leu Ile Glu Cys Val Ile Asn
        35                  40                  45

Lys Asn Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95
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Gln Asn Trp Ile Asp Val Arg Tyr Asp Leu Glu Lys Ile Glu Ser Leu
            100                 105                 110

Ile Gln Ser Ile His Ile Asp Thr Thr Leu Tyr Thr Asp Ser Asp Phe
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Asn Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Leu His Glu Tyr Ser Asn Met Thr Leu Asn Glu Thr Val
145                 150                 155                 160

Arg Asn Val Leu Tyr Leu Ala Asn Ser Thr Leu Ser Ser Asn Lys Asn
                165                 170                 175

Val Ala Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Thr
            180                 185                 190

Phe Thr Glu Phe Leu Gln Ser Phe Ile Arg Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly
                245                 250                 255

Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly His Thr Phe Thr Ser
            260                 265                 270

Tyr Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp
        275                 280                 285

Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys
    290                 295                 300

Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val
305                 310                 315                 320

Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Arg Asp Arg Ala Tyr Gly Gly Ala Gly Asp Tyr Trp Gly Gln
            340                 345                 350

Gly Thr Leu Val Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val
        355                 360                 365

Tyr Pro Leu Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr
    370                 375                 380

Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr
385                 390                 395                 400

Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val
                405                 410                 415

Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser
            420                 425                 430

Ser Thr Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala
        435                 440                 445

Ser Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile
    450                 455                 460

Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Ala Ala Gly Gly
465                 470                 475                 480

Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile
                485                 490                 495

Ser Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp
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            500                 505                 510

Asp Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His
        515                 520                 525

Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg
    530                 535                 540

Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys
545                 550                 555                 560

Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Gly Ala Pro Ile Glu
                565                 570                 575

Arg Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr
            580                 585                 590

Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu
        595                 600                 605

Thr Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp
    610                 615                 620

Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val
625                 630                 635                 640

Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu
                645                 650                 655

Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His
            660                 665                 670

Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro
        675                 680                 685

Gly Lys
    690


<210> SEQ ID NO 182
<211> LENGTH: 690
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mSD15 + m3A7 mHc(T366L/ K392L/T394W) LALAPG

<400> SEQUENCE: 182

Ile Thr Cys Pro Pro Pro Val Ser Ile Glu His Ala Asp Ile Arg Val
1               5                   10                  15

Lys Asn Tyr Ser Val Asn Ser Arg Glu Arg Tyr Val Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Thr Leu Ile Glu Cys Val Ile Asn
        35                  40                  45

Lys Asn Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Ile Asp Val Arg Tyr Asp Leu Glu Lys Ile Glu Ser Leu
            100                 105                 110

Ile Gln Ser Ile His Ile Asp Thr Thr Leu Tyr Thr Asp Ser Asp Phe
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Asn Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Leu His Glu Tyr Ser Asn Met Thr Leu Asn Glu Thr Val
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145                 150                 155                 160

Arg Asn Val Leu Tyr Leu Ala Asn Ser Thr Leu Ser Ser Asn Lys Asn
                165                 170                 175

Val Ala Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Thr
            180                 185                 190

Phe Thr Glu Phe Leu Gln Ser Phe Ile Arg Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly
                245                 250                 255

Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly His Thr Phe Thr Ser
            260                 265                 270

Tyr Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp
        275                 280                 285

Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys
    290                 295                 300

Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val
305                 310                 315                 320

Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Arg Asp Arg Ala Tyr Gly Gly Ala Gly Asp Tyr Trp Gly Gln
            340                 345                 350

Gly Thr Leu Val Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val
        355                 360                 365

Tyr Pro Leu Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr
    370                 375                 380

Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr
385                 390                 395                 400

Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val
                405                 410                 415

Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser
            420                 425                 430

Ser Thr Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala
        435                 440                 445

Ser Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile
    450                 455                 460

Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Ala Ala Gly Gly
465                 470                 475                 480

Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile
                485                 490                 495

Ser Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp
            500                 505                 510

Asp Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His
        515                 520                 525

Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg
    530                 535                 540

Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys
545                 550                 555                 560
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Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Gly Ala Pro Ile Glu
                565                 570                 575

Arg Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr
            580                 585                 590

Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu
        595                 600                 605

Leu Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp
    610                 615                 620

Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr Leu Asn Trp Glu Pro Val
625                 630                 635                 640

Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu
                645                 650                 655

Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His
            660                 665                 670

Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro
        675                 680                 685

Gly Lys
    690


<210> SEQ ID NO 183
<211> LENGTH: 658
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m3A7 mHc LALPG + mSD15

<400> SEQUENCE: 183

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly His Thr Phe Thr Ser Tyr
            20                  25                  30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Arg Ala Tyr Gly Gly Ala Gly Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr
        115                 120                 125

Pro Leu Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu
    130                 135                 140

Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp
145                 150                 155                 160

Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser
            180                 185                 190

Thr Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser
        195                 200                 205
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Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys
    210                 215                 220

Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Ala Ala Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser
                245                 250                 255

Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp
            260                 265                 270

Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr
        275                 280                 285

Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val
    290                 295                 300

Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu
305                 310                 315                 320

Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Gly Ala Pro Ile Glu Arg
                325                 330                 335

Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val
            340                 345                 350

Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr
        355                 360                 365

Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr
    370                 375                 380

Asn Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys
                405                 410                 415

Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu
            420                 425                 430

Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly
        435                 440                 445

Ser Cys Pro Pro Pro Val Ser Ile Glu His Ala Asp Ile Arg Val Lys
    450                 455                 460

Asn Tyr Ser Val Asn Ser Arg Glu Arg Tyr Val Cys Asn Ser Gly Phe
465                 470                 475                 480

Lys Arg Lys Ala Gly Thr Ser Thr Leu Ile Glu Cys Val Ile Asn Lys
                485                 490                 495

Asn Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
            500                 505                 510

Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly Ser
        515                 520                 525

Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Gln
    530                 535                 540

Asn Trp Ile Asp Val Arg Tyr Asp Leu Glu Lys Ile Glu Ser Leu Ile
545                 550                 555                 560

Gln Ser Ile His Ile Asp Thr Thr Leu Tyr Thr Asp Ser Asp Phe His
                565                 570                 575

Pro Ser Cys Lys Val Thr Ala Met Asn Cys Phe Leu Leu Glu Leu Gln
            580                 585                 590

Val Ile Leu His Glu Tyr Ser Asn Met Thr Leu Asn Glu Thr Val Arg
        595                 600                 605
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```
Asn Val Leu Tyr Leu Ala Asn Ser Thr Leu Ser Ser Asn Lys Asn Val
    610                 615                 620

Ala Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Thr Phe
625                 630                 635                 640

Thr Glu Phe Leu Gln Ser Phe Ile Arg Ile Val Gln Met Phe Ile Asn
                645                 650                 655

Thr Ser


<210> SEQ ID NO 184
<211> LENGTH: 658
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: m3A7 mHC(T366L/K392L/T394W) + mSD15 LALAPG

<400> SEQUENCE: 184

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly His Thr Phe Thr Ser Tyr
            20                  25                  30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Arg Ala Tyr Gly Gly Ala Gly Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr
        115                 120                 125

Pro Leu Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu
    130                 135                 140

Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp
145                 150                 155                 160

Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser
            180                 185                 190

Thr Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser
        195                 200                 205

Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys
    210                 215                 220

Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Ala Ala Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser
                245                 250                 255

Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp
            260                 265                 270

Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr
        275                 280                 285

Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val
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    290                 295                 300

Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu
305                 310                 315                 320

Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Gly Ala Pro Ile Glu Arg
                325                 330                 335

Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val
            340                 345                 350

Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Leu
        355                 360                 365

Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr
    370                 375                 380

Asn Asn Gly Lys Thr Glu Leu Asn Tyr Leu Asn Trp Glu Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys
                405                 410                 415

Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu
            420                 425                 430

Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly
        435                 440                 445

Ser Cys Pro Pro Pro Val Ser Ile Glu His Ala Asp Ile Arg Val Lys
    450                 455                 460

Asn Tyr Ser Val Asn Ser Arg Glu Arg Tyr Val Cys Asn Ser Gly Phe
465                 470                 475                 480

Lys Arg Lys Ala Gly Thr Ser Thr Leu Ile Glu Cys Val Ile Asn Lys
                485                 490                 495

Asn Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
            500                 505                 510

Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly Ser
        515                 520                 525

Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Gln
    530                 535                 540

Asn Trp Ile Asp Val Arg Tyr Asp Leu Glu Lys Ile Glu Ser Leu Ile
545                 550                 555                 560

Gln Ser Ile His Ile Asp Thr Thr Leu Tyr Thr Asp Ser Asp Phe His
                565                 570                 575

Pro Ser Cys Lys Val Thr Ala Met Asn Cys Phe Leu Leu Glu Leu Gln
            580                 585                 590

Val Ile Leu His Glu Tyr Ser Asn Met Thr Leu Asn Glu Thr Val Arg
        595                 600                 605

Asn Val Leu Tyr Leu Ala Asn Ser Thr Leu Ser Ser Asn Lys Asn Val
    610                 615                 620

Ala Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Thr Phe
625                 630                 635                 640

Thr Glu Phe Leu Gln Ser Phe Ile Arg Ile Val Gln Met Phe Ile Asn
                645                 650                 655

Thr Ser


<210> SEQ ID NO 185
<211> LENGTH: 445
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: DP47 mHC (L351Y/F405A/Y407V) LALAPG

<400> SEQUENCE: 185

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Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn 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 Lys Gly Ser Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro
        115                 120                 125

Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu Gly Cys Leu Val
    130                 135                 140

Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp Asn Ser Gly Ser
145                 150                 155                 160

Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu
                165                 170                 175

Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser Thr Trp Pro Ser
            180                 185                 190

Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val
        195                 200                 205

Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro Pro
    210                 215                 220

Cys Lys Cys Pro Ala Pro Asn Ala Ala Gly Gly Pro Ser Val Phe Ile
225                 230                 235                 240

Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile
                245                 250                 255

Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln
            260                 265                 270

Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr Gln
        275                 280                 285

Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu
    290                 295                 300

Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Lys
305                 310                 315                 320

Val Asn Asn Lys Asp Leu Gly Ala Pro Ile Glu Arg Thr Ile Ser Lys
                325                 330                 335

Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Tyr Pro Pro Pro
            340                 345                 350

Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Leu Cys Met Val Thr
        355                 360                 365

Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly Lys
    370                 375                 380
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Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val Leu Asp Ser Asp Gly
385                 390                 395                 400

Ser Tyr Ala Met Val Ser Lys Leu Arg Val Glu Lys Lys Asn Trp Val
                405                 410                 415

Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu His Asn
            420                 425                 430

His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 186
<211> LENGTH: 215
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: DP47 mLC

<400> SEQUENCE: 186

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
            20                  25                  30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65                  70                  75                  80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
                85                  90                  95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Ala Asp Ala
            100                 105                 110

Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser
        115                 120                 125

Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp
    130                 135                 140

Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val
145                 150                 155                 160

Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met
                165                 170                 175

Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser
            180                 185                 190

Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys
        195                 200                 205

Ser Phe Asn Arg Asn Glu Cys
    210                 215


<210> SEQ ID NO 187
<211> LENGTH: 686
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mSD15 + DP47 mHC LALAPG

<400> SEQUENCE: 187

Ile Thr Cys Pro Pro Pro Val Ser Ile Glu His Ala Asp Ile Arg Val
1               5                   10                  15
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Lys Asn Tyr Ser Val Asn Ser Arg Glu Arg Tyr Val Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Thr Leu Ile Glu Cys Val Ile Asn
        35                  40                  45

Lys Asn Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Ile Asp Val Arg Tyr Asp Leu Glu Lys Ile Glu Ser Leu
            100                 105                 110

Ile Gln Ser Ile His Ile Asp Thr Thr Leu Tyr Thr Asp Ser Asp Phe
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Asn Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Leu His Glu Tyr Ser Asn Met Thr Leu Asn Glu Thr Val
145                 150                 155                 160

Arg Asn Val Leu Tyr Leu Ala Asn Ser Thr Leu Ser Ser Asn Lys Asn
                165                 170                 175

Val Ala Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Thr
            180                 185                 190

Phe Thr Glu Phe Leu Gln Ser Phe Ile Arg Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Lys Gly Ser Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            340                 345                 350

Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr Pro Leu Ala
        355                 360                 365

Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu Gly Cys Leu
    370                 375                 380

Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp Asn Ser Gly
385                 390                 395                 400

Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp
                405                 410                 415
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Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser Thr Trp Pro
            420                 425                 430

Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys
        435                 440                 445

Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro
    450                 455                 460

Pro Cys Lys Cys Pro Ala Pro Asn Ala Ala Gly Gly Pro Ser Val Phe
465                 470                 475                 480

Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro
                485                 490                 495

Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp Val
            500                 505                 510

Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr
        515                 520                 525

Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala
    530                 535                 540

Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys
545                 550                 555                 560

Lys Val Asn Asn Lys Asp Leu Gly Ala Pro Ile Glu Arg Thr Ile Ser
                565                 570                 575

Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro
            580                 585                 590

Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr Cys Met Val
        595                 600                 605

Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly
    610                 615                 620

Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val Leu Asp Ser Asp
625                 630                 635                 640

Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn Trp
                645                 650                 655

Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu His
            660                 665                 670

Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 188
<211> LENGTH: 686
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mSD15 + DP47 mHC (T366L/K392L/T394W) LALAPG

<400> SEQUENCE: 188

Ile Thr Cys Pro Pro Pro Val Ser Ile Glu His Ala Asp Ile Arg Val
1               5                   10                  15

Lys Asn Tyr Ser Val Asn Ser Arg Glu Arg Tyr Val Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Thr Leu Ile Glu Cys Val Ile Asn
        35                  40                  45

Lys Asn Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80
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Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Ile Asp Val Arg Tyr Asp Leu Glu Lys Ile Glu Ser Leu
            100                 105                 110

Ile Gln Ser Ile His Ile Asp Thr Thr Leu Tyr Thr Asp Ser Asp Phe
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Asn Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Leu His Glu Tyr Ser Asn Met Thr Leu Asn Glu Thr Val
145                 150                 155                 160

Arg Asn Val Leu Tyr Leu Ala Asn Ser Thr Leu Ser Ser Asn Lys Asn
                165                 170                 175

Val Ala Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Thr
            180                 185                 190

Phe Thr Glu Phe Leu Gln Ser Phe Ile Arg Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Lys Gly Ser Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            340                 345                 350

Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr Pro Leu Ala
        355                 360                 365

Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu Gly Cys Leu
    370                 375                 380

Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp Asn Ser Gly
385                 390                 395                 400

Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp
                405                 410                 415

Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser Thr Trp Pro
            420                 425                 430

Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys
        435                 440                 445

Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro
    450                 455                 460

Pro Cys Lys Cys Pro Ala Pro Asn Ala Ala Gly Gly Pro Ser Val Phe
465                 470                 475                 480

Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro
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                485                 490                 495

Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp Val
            500                 505                 510

Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr
        515                 520                 525

Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala
    530                 535                 540

Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys
545                 550                 555                 560

Lys Val Asn Asn Lys Asp Leu Gly Ala Pro Ile Glu Arg Thr Ile Ser
                565                 570                 575

Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro
            580                 585                 590

Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Leu Cys Met Val
        595                 600                 605

Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly
    610                 615                 620

Lys Thr Glu Leu Asn Tyr Leu Asn Trp Glu Pro Val Leu Asp Ser Asp
625                 630                 635                 640

Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn Trp
                645                 650                 655

Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu His
            660                 665                 670

Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 189
<211> LENGTH: 654
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: DP47 mHc LALAPG + mSD15

<400> SEQUENCE: 189

Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn 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 Lys Gly Ser Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro
        115                 120                 125

Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu Gly Cys Leu Val
    130                 135                 140

Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp Asn Ser Gly Ser
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145                 150                 155                 160

Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu
                165                 170                 175

Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser Thr Trp Pro Ser
            180                 185                 190

Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val
        195                 200                 205

Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro Pro
    210                 215                 220

Cys Lys Cys Pro Ala Pro Asn Ala Ala Gly Gly Pro Ser Val Phe Ile
225                 230                 235                 240

Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile
                245                 250                 255

Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln
            260                 265                 270

Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr Gln
        275                 280                 285

Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu
    290                 295                 300

Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Lys
305                 310                 315                 320

Val Asn Asn Lys Asp Leu Gly Ala Pro Ile Glu Arg Thr Ile Ser Lys
                325                 330                 335

Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro
            340                 345                 350

Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr Cys Met Val Thr
        355                 360                 365

Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly Lys
    370                 375                 380

Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val Leu Asp Ser Asp Gly
385                 390                 395                 400

Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn Trp Val
                405                 410                 415

Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu His Asn
            420                 425                 430

His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Ser Cys Pro Pro
        435                 440                 445

Pro Val Ser Ile Glu His Ala Asp Ile Arg Val Lys Asn Tyr Ser Val
    450                 455                 460

Asn Ser Arg Glu Arg Tyr Val Cys Asn Ser Gly Phe Lys Arg Lys Ala
465                 470                 475                 480

Gly Thr Ser Thr Leu Ile Glu Cys Val Ile Asn Lys Asn Thr Asn Val
                485                 490                 495

Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp Pro Ala Leu
            500                 505                 510

Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly Ser Gly Gly Gly Gly
        515                 520                 525

Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Gln Asn Trp Ile Asp
    530                 535                 540

Val Arg Tyr Asp Leu Glu Lys Ile Glu Ser Leu Ile Gln Ser Ile His
545                 550                 555                 560
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Ile Asp Thr Thr Leu Tyr Thr Asp Ser Asp Phe His Pro Ser Cys Lys
                565                 570                 575

Val Thr Ala Met Asn Cys Phe Leu Leu Glu Leu Gln Val Ile Leu His
            580                 585                 590

Glu Tyr Ser Asn Met Thr Leu Asn Glu Thr Val Arg Asn Val Leu Tyr
        595                 600                 605

Leu Ala Asn Ser Thr Leu Ser Ser Asn Lys Asn Val Ala Glu Ser Gly
    610                 615                 620

Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Thr Phe Thr Glu Phe Leu
625                 630                 635                 640

Gln Ser Phe Ile Arg Ile Val Gln Met Phe Ile Asn Thr Ser
                645                 650


<210> SEQ ID NO 190
<211> LENGTH: 654
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: DP47 mHC (T366L/K392L/T394W) LALAPG + mSD15

<400> SEQUENCE: 190

Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn 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 Lys Gly Ser Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro
        115                 120                 125

Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu Gly Cys Leu Val
    130                 135                 140

Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp Asn Ser Gly Ser
145                 150                 155                 160

Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu
                165                 170                 175

Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser Thr Trp Pro Ser
            180                 185                 190

Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val
        195                 200                 205

Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro Pro
    210                 215                 220

Cys Lys Cys Pro Ala Pro Asn Ala Ala Gly Gly Pro Ser Val Phe Ile
225                 230                 235                 240

Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile
                245                 250                 255
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Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln
            260                 265                 270

Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr Gln
        275                 280                 285

Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu
    290                 295                 300

Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Lys
305                 310                 315                 320

Val Asn Asn Lys Asp Leu Gly Ala Pro Ile Glu Arg Thr Ile Ser Lys
                325                 330                 335

Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro
            340                 345                 350

Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Leu Cys Met Val Thr
        355                 360                 365

Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly Lys
    370                 375                 380

Thr Glu Leu Asn Tyr Leu Asn Trp Glu Pro Val Leu Asp Ser Asp Gly
385                 390                 395                 400

Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn Trp Val
                405                 410                 415

Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu His Asn
            420                 425                 430

His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Ser Cys Pro Pro
        435                 440                 445

Pro Val Ser Ile Glu His Ala Asp Ile Arg Val Lys Asn Tyr Ser Val
    450                 455                 460

Asn Ser Arg Glu Arg Tyr Val Cys Asn Ser Gly Phe Lys Arg Lys Ala
465                 470                 475                 480

Gly Thr Ser Thr Leu Ile Glu Cys Val Ile Asn Lys Asn Thr Asn Val
                485                 490                 495

Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp Pro Ala Leu
            500                 505                 510

Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly Ser Gly Gly Gly Gly
        515                 520                 525

Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Gln Asn Trp Ile Asp
    530                 535                 540

Val Arg Tyr Asp Leu Glu Lys Ile Glu Ser Leu Ile Gln Ser Ile His
545                 550                 555                 560

Ile Asp Thr Thr Leu Tyr Thr Asp Ser Asp Phe His Pro Ser Cys Lys
                565                 570                 575

Val Thr Ala Met Asn Cys Phe Leu Leu Glu Leu Gln Val Ile Leu His
            580                 585                 590

Glu Tyr Ser Asn Met Thr Leu Asn Glu Thr Val Arg Asn Val Leu Tyr
        595                 600                 605

Leu Ala Asn Ser Thr Leu Ser Ser Asn Lys Asn Val Ala Glu Ser Gly
    610                 615                 620

Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Thr Phe Thr Glu Phe Leu
625                 630                 635                 640

Gln Ser Phe Ile Arg Ile Val Gln Met Phe Ile Asn Thr Ser
                645                 650
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<210> SEQ ID NO 191
<211> LENGTH: 445
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: DP47 HC (T350V/T366L/K392L/T394W) LALAPG

<400> SEQUENCE: 191

Glu Val Gln Leu Leu 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 Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn 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 Lys Gly Ser Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
115 120 125

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
130 135 140

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145 150 155 160

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
165 170 175

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
180 185 190

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
195 200 205

Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
210 215 220

Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu
225 230 235 240

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
245 250 255

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
260 265 270

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
275 280 285

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
290 295 300

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
305 310 315 320

Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys
325 330 335

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro Pro Ser
340 345 350

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Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys Leu Val Lys
        355                 360                 365

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
    370                 375                 380

Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser Asp Gly
385                 390                 395                 400

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
                405                 410                 415

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
            420                 425                 430

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 192
<211> LENGTH: 215
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: DP47 LC

<400> SEQUENCE: 192

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
            20                  25                  30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65                  70                  75                  80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
                85                  90                  95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
            100                 105                 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
        115                 120                 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
                165                 170                 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180                 185                 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
        195                 200                 205

Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 193
<211> LENGTH: 686
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: hSD15 + DP47 HC LALPG

<400> SEQUENCE: 193

```
Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                  10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Lys Gly Ser Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            340                 345                 350

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        355                 360                 365

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
    370                 375                 380
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Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
385                 390                 395                 400

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                405                 410                 415

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            420                 425                 430

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        435                 440                 445

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
    450                 455                 460

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
465                 470                 475                 480

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                485                 490                 495

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            500                 505                 510

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        515                 520                 525

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
    530                 535                 540

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
545                 550                 555                 560

Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser
                565                 570                 575

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            580                 585                 590

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        595                 600                 605

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    610                 615                 620

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
625                 630                 635                 640

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                645                 650                 655

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            660                 665                 670

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 194
<211> LENGTH: 686
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hSD15 + DP47 HC (T350V/L351Y/F405A/Y407V)
      LALAPG

<400> SEQUENCE: 194

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45
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Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Lys Gly Ser Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            340                 345                 350

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        355                 360                 365

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
    370                 375                 380

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
385                 390                 395                 400

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                405                 410                 415

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            420                 425                 430

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        435                 440                 445
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Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
    450                 455                 460

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
465                 470                 475                 480

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                485                 490                 495

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            500                 505                 510

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        515                 520                 525

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
    530                 535                 540

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
545                 550                 555                 560

Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser
                565                 570                 575

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro
            580                 585                 590

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        595                 600                 605

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    610                 615                 620

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
625                 630                 635                 640

Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                645                 650                 655

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            660                 665                 670

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 195
<211> LENGTH: 654
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: DP47 HC +LALAPG hSD15

<400> SEQUENCE: 195

Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn 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 Lys Gly Ser Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110
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```
Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
        115                 120                 125

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
    130                 135                 140

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145                 150                 155                 160

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
                165                 170                 175

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
            180                 185                 190

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
        195                 200                 205

Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
    210                 215                 220

Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu
225                 230                 235                 240

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
                245                 250                 255

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
            260                 265                 270

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
        275                 280                 285

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
    290                 295                 300

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
305                 310                 315                 320

Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys
                325                 330                 335

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
            340                 345                 350

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
        355                 360                 365

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
    370                 375                 380

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
385                 390                 395                 400

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
                405                 410                 415

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
            420                 425                 430

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ser Cys Pro Pro
        435                 440                 445

Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu
    450                 455                 460

Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala
465                 470                 475                 480

Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val
                485                 490                 495

Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp Pro Ala Leu
            500                 505                 510

Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly Ser Gly Gly Gly Gly
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        515                 520                 525

Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Gln Asn Trp Val Asn
    530                 535                 540

Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His
545                 550                 555                 560

Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys
                565                 570                 575

Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu
            580                 585                 590

Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile
        595                 600                 605

Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly
    610                 615                 620

Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu
625                 630                 635                 640

Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser
                645                 650


<210> SEQ ID NO 196
<211> LENGTH: 654
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: DP47 HC (T350V/L351Y/F405A/Y407V) LALAPG +
      hSD15

<400> SEQUENCE: 196

Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn 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 Lys Gly Ser Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
        115                 120                 125

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
    130                 135                 140

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145                 150                 155                 160

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
                165                 170                 175

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
            180                 185                 190

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
        195                 200                 205
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```
Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
    210                 215                 220

Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu
225                 230                 235                 240

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
                245                 250                 255

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
            260                 265                 270

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
        275                 280                 285

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
    290                 295                 300

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
305                 310                 315                 320

Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys
                325                 330                 335

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser
            340                 345                 350

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
        355                 360                 365

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
    370                 375                 380

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
385                 390                 395                 400

Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
                405                 410                 415

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
            420                 425                 430

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ser Cys Pro Pro
        435                 440                 445

Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu
    450                 455                 460

Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala
465                 470                 475                 480

Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val
                485                 490                 495

Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp Pro Ala Leu
            500                 505                 510

Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly Ser Gly Gly Gly Gly
        515                 520                 525

Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Gln Asn Trp Val Asn
    530                 535                 540

Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His
545                 550                 555                 560

Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys
                565                 570                 575

Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu
            580                 585                 590

Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile
        595                 600                 605

Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly
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    610                 615                 620

Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu
625                 630                 635                 640

Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser
                645                 650


<210> SEQ ID NO 197
<211> LENGTH: 686
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: N65A-hSD15 + DP47 HC (T350V/L351Y/F405A/Y407V)
      LALAPG

<400> SEQUENCE: 197

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Ala Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300
```

-continued

```
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Lys Gly Ser Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            340                 345                 350

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        355                 360                 365

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
    370                 375                 380

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
385                 390                 395                 400

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                405                 410                 415

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            420                 425                 430

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        435                 440                 445

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
    450                 455                 460

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
465                 470                 475                 480

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                485                 490                 495

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            500                 505                 510

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        515                 520                 525

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
    530                 535                 540

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
545                 550                 555                 560

Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser
                565                 570                 575

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro
            580                 585                 590

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        595                 600                 605

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    610                 615                 620

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
625                 630                 635                 640

Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                645                 650                 655

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            660                 665                 670

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 198
<211> LENGTH: 686
<212> TYPE: PRT
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: N65D-hSD15 + DP47 HC (T350V/L351Y/F405A/Y407V)
LALAPG

<400> SEQUENCE: 198

```
Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Asp Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Lys Gly Ser Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            340                 345                 350

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        355                 360                 365
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Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
    370                 375                 380

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
385                 390                 395                 400

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                405                 410                 415

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            420                 425                 430

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        435                 440                 445

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
    450                 455                 460

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
465                 470                 475                 480

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                485                 490                 495

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            500                 505                 510

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        515                 520                 525

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
    530                 535                 540

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
545                 550                 555                 560

Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser
                565                 570                 575

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro
            580                 585                 590

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        595                 600                 605

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    610                 615                 620

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
625                 630                 635                 640

Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                645                 650                 655

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            660                 665                 670

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 199
<211> LENGTH: 686
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: N65S-hSD15 + DP47 HC (T350V/L351Y/F405A/Y407V)
      LALAPG

<400> SEQUENCE: 199

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30
```

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Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Ser Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Lys Gly Ser Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            340                 345                 350

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        355                 360                 365

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
    370                 375                 380

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
385                 390                 395                 400

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                405                 410                 415

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            420                 425                 430
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```
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        435                 440                 445

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
    450                 455                 460

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
465                 470                 475                 480

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                485                 490                 495

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            500                 505                 510

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        515                 520                 525

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
    530                 535                 540

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
545                 550                 555                 560

Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser
                565                 570                 575

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro
            580                 585                 590

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        595                 600                 605

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    610                 615                 620

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
625                 630                 635                 640

Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                645                 650                 655

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            660                 665                 670

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 200
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D7A8 VH

<400> SEQUENCE: 200

Glu Val Gln Leu Leu 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 Ser Ala Tyr
            20                  25                  30

Arg Met Phe Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Tyr Pro Ser Gly Gly Ile Thr Phe Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95
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Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 201
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D7A8 full length HC

<400> SEQUENCE: 201

Glu Val Gln Leu Leu 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 Ser Ala Tyr
            20                  25                  30

Arg Met Phe Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Tyr Pro Ser Gly Gly Ile Thr Phe Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val 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 Arg 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
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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 Glu Glu Met 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 202
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D7A8 HC (S354C/T366W) LALA

<400> SEQUENCE: 202

Glu Val Gln Leu Leu 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 Ser Ala Tyr
            20                  25                  30

Arg Met Phe Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Tyr Pro Ser Gly Gly Ile Thr Phe Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val 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
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```
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala 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 Cys Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Trp 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 203
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D7A8 HC (T350V/ T366L/ K392L/ T394W) LALA

<400> SEQUENCE: 203

Glu Val Gln Leu Leu 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 Ser Ala Tyr
            20                  25                  30

Arg Met Phe Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Tyr Pro Ser Gly Gly Ile Thr Phe Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95
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```
Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val 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 Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala 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 Leu Pro Pro Ser Arg Glu Glu Met 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 204
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D7A8 VL

-continued

<400> SEQUENCE: 204

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ala Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Thr Arg Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Gln
100 105 110

Pro

<210> SEQ ID NO 205
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D7A8 full length LC

<400> SEQUENCE: 205

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ala Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Thr Arg Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys
145 150 155 160

Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205

Thr Val Ala Pro Thr Glu Cys Ser

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    210                 215


<210> SEQ ID NO 206
<211> LENGTH: 681
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hSD15 + D7A8 HC LALA

<400> SEQUENCE: 206

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly
225                 230                 235                 240

Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser
                245                 250                 255

Gly Phe Thr Phe Ser Ala Tyr Arg Met Phe Trp Val Arg Gln Ala Pro
            260                 265                 270

Gly Lys Gly Leu Glu Trp Val Ser Ser Ile Tyr Pro Ser Gly Gly Ile
        275                 280                 285

Thr Phe Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
    290                 295                 300

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
305                 310                 315                 320

Asp Thr Ala Ile Tyr Tyr Cys Ala Arg Ile Lys Leu Gly Thr Val Thr
                325                 330                 335

Thr Val Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
```

-continued

```
            340                 345                 350

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
        355                 360                 365

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
    370                 375                 380

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
385                 390                 395                 400

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
                405                 410                 415

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
            420                 425                 430

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg
        435                 440                 445

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
    450                 455                 460

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
465                 470                 475                 480

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
                485                 490                 495

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
            500                 505                 510

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
        515                 520                 525

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
    530                 535                 540

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
545                 550                 555                 560

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
                565                 570                 575

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
            580                 585                 590

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
        595                 600                 605

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
    610                 615                 620

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
625                 630                 635                 640

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
                645                 650                 655

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
            660                 665                 670

Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680


<210> SEQ ID NO 207
<211> LENGTH: 681
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hSD15 + D7A8HC (Y349C/T366S/L368A/Y407V) LALA

<400> SEQUENCE: 207

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
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1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly
225                 230                 235                 240

Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser
                245                 250                 255

Gly Phe Thr Phe Ser Ala Tyr Arg Met Phe Trp Val Arg Gln Ala Pro
            260                 265                 270

Gly Lys Gly Leu Glu Trp Val Ser Ser Ile Tyr Pro Ser Gly Gly Ile
        275                 280                 285

Thr Phe Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
    290                 295                 300

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
305                 310                 315                 320

Asp Thr Ala Ile Tyr Tyr Cys Ala Arg Ile Lys Leu Gly Thr Val Thr
                325                 330                 335

Thr Val Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
            340                 345                 350

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
        355                 360                 365

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
    370                 375                 380

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
385                 390                 395                 400

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
                405                 410                 415
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Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
            420                 425                 430

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg
        435                 440                 445

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
    450                 455                 460

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
465                 470                 475                 480

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
                485                 490                 495

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
            500                 505                 510

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
        515                 520                 525

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
    530                 535                 540

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
545                 550                 555                 560

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
                565                 570                 575

Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met
            580                 585                 590

Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro
        595                 600                 605

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
    610                 615                 620

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
625                 630                 635                 640

Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
                645                 650                 655

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
            660                 665                 670

Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680


<210> SEQ ID NO 208
<211> LENGTH: 681
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hSD15 + D7A8HC (T350V/L351Y/F405A/Y407V) LALA

<400> SEQUENCE: 208

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80
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Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly
225                 230                 235                 240

Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser
                245                 250                 255

Gly Phe Thr Phe Ser Ala Tyr Arg Met Phe Trp Val Arg Gln Ala Pro
            260                 265                 270

Gly Lys Gly Leu Glu Trp Val Ser Ser Ile Tyr Pro Ser Gly Gly Ile
        275                 280                 285

Thr Phe Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
    290                 295                 300

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
305                 310                 315                 320

Asp Thr Ala Ile Tyr Tyr Cys Ala Arg Ile Lys Leu Gly Thr Val Thr
                325                 330                 335

Thr Val Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
            340                 345                 350

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
        355                 360                 365

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
    370                 375                 380

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
385                 390                 395                 400

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
                405                 410                 415

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
            420                 425                 430

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg
        435                 440                 445

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
    450                 455                 460

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
465                 470                 475                 480
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Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
                485                 490                 495

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
            500                 505                 510

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
        515                 520                 525

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
    530                 535                 540

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
545                 550                 555                 560

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
                565                 570                 575

Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Glu Glu Met
            580                 585                 590

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
        595                 600                 605

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
    610                 615                 620

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Ala Leu
625                 630                 635                 640

Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
                645                 650                 655

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
            660                 665                 670

Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680


<210> SEQ ID NO 209
<211> LENGTH: 659
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D7A8 HC LALA + hSD15

<400> SEQUENCE: 209

Glu Val Gln Leu Leu 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 Ser Ala Tyr
            20                  25                  30

Arg Met Phe Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Tyr Pro Ser Gly Gly Ile Thr Phe Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val 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
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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 Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala 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 Glu Glu Met 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 Ser Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
    450                 455                 460

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
465                 470                 475                 480

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
                485                 490                 495

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
            500                 505                 510

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
        515                 520                 525

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
    530                 535                 540

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
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545 550 555 560

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
565 570 575

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
580 585 590

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
595 600 605

Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
610 615 620

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
625 630 635 640

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
645 650 655

Asn Thr Ser

<210> SEQ ID NO 210
<211> LENGTH: 658
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D7A8 HC (Y349C/T366S/L368A/Y407V) LALA+ hSD15

<400> SEQUENCE: 210

Glu Val Gln Leu Leu 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 Ser Ala Tyr
20 25 30

Arg Met Phe Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Tyr Pro Ser Gly Gly Ile Thr Phe Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val 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 Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala 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 Cys
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Ser Cys Ala 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 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 Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys
    450                 455                 460

Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe
465                 470                 475                 480

Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys
                485                 490                 495

Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
            500                 505                 510

Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly Ser
        515                 520                 525

Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Gln
    530                 535                 540

Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
545                 550                 555                 560

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
                565                 570                 575

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
            580                 585                 590

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
        595                 600                 605

Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
    610                 615                 620

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
625                 630                 635                 640
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```
Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
                645                 650                 655

Thr Ser


<210> SEQ ID NO 211
<211> LENGTH: 658
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D7A8 HC (T350V/L351Y/F405A/Y407V) LALA+ hSD15

<400> SEQUENCE: 211

Glu Val Gln Leu Leu 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 Ser Ala Tyr
            20                  25                  30

Arg Met Phe Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Tyr Pro Ser Gly Gly Ile Thr Phe Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val 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 Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala 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
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               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 Glu Glu Met 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 Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys
    450                 455                 460

Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe
465                 470                 475                 480

Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys
                485                 490                 495

Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
            500                 505                 510

Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly Ser
        515                 520                 525

Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Gln
    530                 535                 540

Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
545                 550                 555                 560

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
                565                 570                 575

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
            580                 585                 590

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
        595                 600                 605

Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
    610                 615                 620

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
625                 630                 635                 640

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
                645                 650                 655

Thr Ser


<210> SEQ ID NO 212
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Human IL-15 (mature protein, residue N65 is in
      bold)

<400> SEQUENCE: 212

Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
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1               5                   10                  15

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
            20                  25                  30

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
        35                  40                  45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
    50                  55                  60

Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65                  70                  75                  80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
                85                  90                  95

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
            100                 105                 110

Thr Ser


<210> SEQ ID NO 213
<211> LENGTH: 266
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Human IL-15 R? subunit (signal peptide is
      underlined, residue N60 is in bold)

<400> SEQUENCE: 213

Met Ala Pro Arg Arg Ala Arg Gly Cys Arg Thr Leu Gly Leu Pro Ala
1               5                   10                  15

Leu Leu Leu Leu Leu Leu Leu Arg Pro Pro Ala Thr Arg Gly Ile Thr
            20                  25                  30

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
        35                  40                  45

Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys
    50                  55                  60

Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala
65                  70                  75                  80

Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp
                85                  90                  95

Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr Thr
            100                 105                 110

Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys Glu
        115                 120                 125

Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr Ala
    130                 135                 140

Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser Thr
145                 150                 155                 160

Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro Ser
                165                 170                 175

Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His Gln
            180                 185                 190

Pro Pro Gly Val Tyr Pro Gln His Ser Asp Thr Thr Val Ala Ile Ser
        195                 200                 205

Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu Leu Ala
    210                 215                 220

Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val Glu Met
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225 230 235 240

Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser Arg Asp
245 250 255

Glu Asp Leu Glu Asn Cys Ser His His Leu
260 265

<210> SEQ ID NO 214
<211> LENGTH: 61
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IL-15R? sushi domain

<400> SEQUENCE: 214

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
1 5 10 15

Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys
20 25 30

Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala
35 40 45

Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys
50 55 60

<210> SEQ ID NO 215
<211> LENGTH: 34
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Linker 1

<400> SEQUENCE: 215

Ile Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly
1 5 10 15

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25 30

Leu Gln

<210> SEQ ID NO 216
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Linker 2

<400> SEQUENCE: 216

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25 30

<210> SEQ ID NO 217
<211> LENGTH: 34
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Exemplary linker

<400> SEQUENCE: 217

Ile Arg Asp Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

-continued

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly

<210> SEQ ID NO 218
<211> LENGTH: 34
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Exemplary linker

<400> SEQUENCE: 218

Ile Arg Asp Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
1 5 10 15

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
20 25 30

Gly Ser

<210> SEQ ID NO 219
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38B2 LC

<400> SEQUENCE: 219

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 Glu Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu Ser 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 Gly Asp Ser Phe Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu 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 220
<211> LENGTH: 447
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38B2 HC1-1 (T350V/T366L/K392L/T394W) LALAPG

<400> SEQUENCE: 220

Glu Val Gln Leu Leu 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 Ser Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn 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 Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro
340 345 350

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Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Leu Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 221
<211> LENGTH: 447
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38B2 HC1-2 (T350V/L351Y/F405A/Y407V) LALAPG

<400> SEQUENCE: 221

Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn 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 Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr Thr
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255
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```
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro
            340                 345                 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 222
<211> LENGTH: 447
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38B2 HC1-3 (CW-CSAV) S354C/T366W LALAPG

<400> SEQUENCE: 222

Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn 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 Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr Thr
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160
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```
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 223
<211> LENGTH: 447
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38B2 HC1-4 (CW-CSAV) Y349C/T366S/L368A/Y407V
      LALAPG

<400> SEQUENCE: 223

Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
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```
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn 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 Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr Thr
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro
            340                 345                 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445
```

<210> SEQ ID NO 224
<211> LENGTH: 688

-continued

<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 65N-38B2 HC2-1 (T350V/L351Y/F405A/Y407V) LALAPG

<400> SEQUENCE: 224

```
Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                  10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365
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```
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
            580                 585                 590

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
        595                 600                 605

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 225
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 65N-38B2 HC2-2   (T350V/ T366L/K392L/T394W)
      LALAPG

<400> SEQUENCE: 225

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30
```

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```
Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430
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```
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu
            580                 585                 590

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Leu Cys
        595                 600                 605

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 226
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 65N-38B2 HC2-3 (CW-CSAV) Y349C/T366S/L368A/
      Y407V LALAPG

<400> SEQUENCE: 226

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95
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```
Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495
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Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu
            580                 585                 590

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys
        595                 600                 605

Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 227
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 65N-38B2 HC2-4 S354C/T366W LALAPG

<400> SEQUENCE: 227

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160
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Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
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               565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            580                 585                 590

Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys
        595                 600                 605

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 228
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 65S-38B2 HC2-1 (T350V/L351Y/F405A/Y407V) LALAPG

<400> SEQUENCE: 228

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Ser Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
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225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
            580                 585                 590

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
        595                 600                 605

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640
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Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 229
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 65S-38B2 HC2-2 (T350V/T366L/K392L/T394W) LALAPG

<400> SEQUENCE: 229

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Ser Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300
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Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu
            580                 585                 590

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Leu Cys
        595                 600                 605

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 230
<211> LENGTH: 688
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 65S-38B2 HC2-3 (CW-CSAV) Y349C/T366S/L368A/
Y407V LALAP

<400> SEQUENCE: 230

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1 5 10 15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
20 25 30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
35 40 45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
50 55 60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65 70 75 80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
85 90 95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
100 105 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
115 120 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
130 135 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145 150 155 160

Glu Ser Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
165 170 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
180 185 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
195 200 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
210 215 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225 230 235 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
245 250 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
260 265 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
275 280 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
290 295 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305 310 315 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
325 330 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
340 345 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
355 360 365

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Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu
            580                 585                 590

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys
        595                 600                 605

Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 231
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 65S-38B2 HC2-4 S354C/T366W LALAPG

<400> SEQUENCE: 231

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30
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Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Ser Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430
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Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            580                 585                 590

Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys
        595                 600                 605

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 232
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 65D-38B2 HC2-1 (T350V/L351Y/F405A/Y407V) LALAPG

<400> SEQUENCE: 232

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95
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```
Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Asp Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
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            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
            580                 585                 590

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
        595                 600                 605

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 233
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 65D-38B2 HC2-2 (T350V/T366L/K392L/T394W) LALAPG

<400> SEQUENCE: 233

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Asp Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
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                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575
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Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu
            580                 585                 590

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Leu Cys
        595                 600                 605

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 234
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 65D-38B2 HC2-3 (CW-CSAV) Y349C/T366S/L368A/
      Y407V LALAPG

<400> SEQUENCE: 234

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Asp Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
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225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu
            580                 585                 590

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys
        595                 600                 605

Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640
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Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 235
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 65D-38B2 HC2-4 S354C/ T366W LALAPG

<400> SEQUENCE: 235

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Asp Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300
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Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            580                 585                 590

Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys
        595                 600                 605

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 236
<211> LENGTH: 688
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 65S-38B2 HC2-5 (T350V/L351Y/F405A/Y407V) LALAPG

<400> SEQUENCE: 236

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1 5 10 15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
20 25 30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
35 40 45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
50 55 60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65 70 75 80

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly
85 90 95

Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
100 105 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
115 120 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
130 135 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145 150 155 160

Glu Ser Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
165 170 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
180 185 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
195 200 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
210 215 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225 230 235 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
245 250 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
260 265 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
275 280 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
290 295 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305 310 315 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
325 330 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
340 345 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
355 360 365

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Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr
            580                 585                 590

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
        595                 600                 605

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 237
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 65S-38B2 HC2-6 (T350V/T366L/K392L/T394W) LALAPG

<400> SEQUENCE: 237

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30
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Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly
                85                  90                  95

Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Ser Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
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        435                 440                 445

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu
            580                 585                 590

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Leu Cys
        595                 600                 605

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 238
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 65S-38B2 HC2-7 (CW-CSAV) Y349C/T366S/L368A/
      Y407V LALAPG

<400> SEQUENCE: 238

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly
                85                  90                  95
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Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Ser Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
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            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu
            580                 585                 590

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys
        595                 600                 605

Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 239
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 65S-38B2 HC2-8 S354C/T366W LALAPG

<400> SEQUENCE: 239

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly
                85                  90                  95

Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Ser Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
```

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                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr
                565                 570                 575
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Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            580                 585                 590

Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys
        595                 600                 605

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 240
<211> LENGTH: 447
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 38B2 HC1-3B (CW-CSAV) S354C/T366W LALA

<400> SEQUENCE: 240

Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn 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 Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr Thr
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225                 230                 235                 240
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```
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 241
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 65S-38B2 HC2-3B (CW-CSAV) Y349C/T366S/L368A/
      Y407V LALA

<400> SEQUENCE: 241

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
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    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Ser Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540
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Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu
            580                 585                 590

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys
        595                 600                 605

Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 242
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 65S-38B2 HC2-7B (CW-CSAV) Y349C/T366S/L368A/
      Y407V LALA

<400> SEQUENCE: 242

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly
                85                  90                  95

Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Ser Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
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```
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu
            580                 585                 590

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys
        595                 600                 605
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```
Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640

Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 243
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 65D-38B2 HC2-3B (CW-CSAV) Y349C/T366S/L368A/
      Y407V LALA

<400> SEQUENCE: 243

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Gly Gly
65                  70                  75                  80

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
                85                  90                  95

Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
            100                 105                 110

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
        115                 120                 125

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
    130                 135                 140

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
145                 150                 155                 160

Glu Asp Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
                165                 170                 175

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
            180                 185                 190

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
        195                 200                 205

Asn Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
                245                 250                 255

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
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```
            260                 265                 270

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        275                 280                 285

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
    290                 295                 300

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
305                 310                 315                 320

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                325                 330                 335

Cys Ala Ser Ser Pro Leu Gln Trp Val Asp Val Trp Gly Gln Gly Thr
            340                 345                 350

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        355                 360                 365

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    370                 375                 380

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
385                 390                 395                 400

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                405                 410                 415

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            420                 425                 430

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        435                 440                 445

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    450                 455                 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
465                 470                 475                 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                485                 490                 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            500                 505                 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        515                 520                 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    530                 535                 540

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu
            580                 585                 590

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys
        595                 600                 605

Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640
```

-continued

```
Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser
                645                 650                 655

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685


<210> SEQ ID NO 244
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Exemplary linker

<400> SEQUENCE: 244

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1               5                   10                  15

Gly Gly Gly Ser
            20
```

1-76. (canceled)

77. An anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein:

a. the sequences of CDR1H, CDR2H and CDR3H comprise SEQ ID NOS: 21, 22, and 23; and

b. the sequences of CDR1L, CDR2L and CDR3L comprise:

i. SEQ ID NOS: 96, 97 and 82

ii. SEQ ID NOS: 45, 46, and 47;

iii. SEQ ID NOS: 66, 67, and 68;

iv. SEQ ID NOS: 70, 67, and 71;

v. SEQ ID NOS: 73, 74, and 75;

vi. SEQ ID NOS: 77, 78, and 47;

vii. SEQ ID NOS: 80, 81, and 82;

viii. SEQ ID NOS: 77, 78, and 84;

ix. SEQ ID NOS: 77, 86, and 47;

x. SEQ ID NOS: 88, 89, and 47;

xi. SEQ ID NOS: 66, 67, and 47;

xii. SEQ ID NOS: 80, 92, and 75;

xiii. SEQ ID NOS: 80, 94, and 71;

xiv. SEQ ID NOS: 99, 100, and 47;

xv. SEQ ID NOS: 102, 103, and 104;

xvi. SEQ ID NOS: 106, 103, and 47;

xvii. SEQ ID NOS: 108, 103, and 47;

xviii. SEQ ID NOS: 110, 111, and 75;

xix. SEQ ID NOS: 77, 103, and 113;

xx. SEQ ID NOS: 77, 111, and 47;

xxi. SEQ ID NOS: 116, 67, and 47;

xxii. SEQ ID NOS: 118, 119, and 47;

xxiii. SEQ ID NOS: 80, 78, and 47;

xxiv. SEQ ID NOS: 122, 103 and 47;

xxv. SEQ ID NOS: 124, 125, and 75;

xxvi. SEQ ID NOS: 127, 38, and 68;

xxvii. SEQ ID NOS: 129, 130, and 47; or

xxviii. SEQ ID NOS: 132, 133, and 75.

78. The anti-PD-1 antibody, or an antigen-binding fragment thereof, of claim **77**, wherein:

a. the heavy chain variable region comprises:

i. SEQ ID NO: 24, or

ii. a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 24; and

b. the light chain variable region comprises:

i. SEQ ID NO: 48, 69, 72, 76, 79, 83, 85, 87, 90, 91, 93, 95, 98, 101, 105, 107, 109, 112, 114, 115, 117, 120, 121, 123, 126, 128, 131, or 134, or

ii. a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any of SEQ ID NO: 48, 69, 72, 76, 79, 83, 85, 87, 90, 91, 93, 95, 98, 101, 105, 107, 109, 112, 114, 115, 117, 120, 121, 123, 126, 128, 131, or 134.

79. The anti-PD-1 antibody, or an antigen-binding fragment thereof, of claim **77**, wherein:

the sequence of CDR1H comprises the sequence of SEQ ID NO: 21;

the sequence of CDR2H comprises the sequence of SEQ ID NO: 22;

the sequence of CDR3H comprises the sequence of SEQ ID NO: 23

the sequence of CDR1L comprises the sequence of SEQ ID NO: 96;

the sequence of CDR2L comprises the sequence of SEQ ID NO: 97; and

the sequence of CDR3L comprises the sequence of SEQ ID NO: 82.

80. The anti-PD-1 antibody, or an antigen-binding fragment thereof, of claim **79**, wherein:

a. the heavy chain variable region comprises SEQ ID NO: 24, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 24; and

b. the light chain variable region comprises SEQ ID NO: 98, or a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 98.

81. An anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein:

a. the sequences of CDR1H, CDR2H and CDR3H comprise SEQ ID NOS: 17, 18, and 19; and

b. the sequences of CDR1L, CDR2L and CDR3L comprise:

i. SEQ ID NOS: 41, 49, and 50;

ii. SEQ ID NOS: 41, 42, and 43;

iii. SEQ ID NOS: 41, 52, and 53;

iv. SEQ ID NOS: 41, 55, and 56; or

v. SEQ ID NOS: 58, 59, and 60.

82. The anti-PD-1 antibody, or an antigen-binding fragment thereof, of claim **81**, wherein:

a. the heavy chain variable region comprises:

i. SEQ ID NO: 20, or

ii. a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 20; and

b. the light chain variable region comprises:

i. SEQ ID NO: 44, 51, 54, 57, or 61, or

ii. a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NO: 44, 51, 54, 57, or 61.

83. The anti-PD-1 antibody, or an antigen-binding fragment thereof, of claim **77**, wherein the antibody or antigen-binding fragment is a multispecific or a bispecific antibody or antigen-binding fragment thereof.

84. The anti-PD-1 antibody, or an antigen-binding fragment thereof, of claim **77**, wherein the antibody or antigen-binding fragment is an scFv, Fv, Fab', Fab, F(ab')2, or diabody.

85. The anti-PD-1 antibody, or an antigen-binding fragment thereof, of claim **77**, wherein the antibody is an IgG class immunoglobulin, optionally having isotype IgG1 or IgG4.

86. The anti-PD-1 antibody, or an antigen-binding fragment thereof, of claim **77**, wherein the antibody or antigen-binding fragment comprises a first and a second heavy chain constant region, and wherein the antibody or antigen-binding fragment thereof comprises at least one modification in the CH3 domains of the first and the second heavy chain causing heterodimerization.

87. The anti-PD-1 antibody, or an antigen-binding fragment thereof, of claim **86**, wherein:

a. the CH3 domain of the first heavy chain comprises one or more of amino acid substitutions S354C and T366W; and the CH3 domain of the second heavy chain comprises one or more of amino acid substitutions Y349C, T366S, L368A, and Y407V;

b. the CH3 domain of the first heavy chain comprises one or more of amino acid substitutions T350V, L351Y, F405A, and Y407V; and the CH3 domain of the second heavy chain comprises one or more of amino acid substitutions T350V, T366L, K392L, and T394W; or

c. the CH3 domain of the first heavy chain comprises one or more of amino acid substitutions L351Y, F405A, and Y407V; and the CH3 domain of the second heavy chain comprises one or more of amino acid substitutions T366L, K392L, and T394W (Kabat EU index numbering).

88. The anti-PD-1 antibody, or an antigen-binding fragment thereof, of claim **86**, wherein the Fc domain, if present, comprises one or more amino acid substitution that reduces binding to an Fc receptor or reduces effector function, wherein the one or more amino acid substitution is selected from L234A, L235A, and P329G (Kabat EU index numbering).

89. A fusion protein comprising:

a. the anti-PD-1 antibody, or an antigen-binding fragment thereof, of claim **77**;

b. an IL-15Rα sushi domain polypeptide comprising the amino acid sequence of SEQ ID NO: 214, or an amino acid sequence that is at least 95% identical to SEQ ID NO:

214;

c. an IL-15 polypeptide comprising the amino acid sequence of SEQ ID NO: 212, or an amino acid sequence that is at least 90% or at least 95% identical to SEQ ID NO: 212; and

d. a first linker polypeptide joining the IL-15Rα sushi domain polypeptide and the IL-15 polypeptide, optionally wherein the IL-15Rα sushi domain polypeptide is fused to the N-terminus of the IL-15 polypeptide.

90. The fusion protein of claim **89**, wherein (i) the IL-15Rα sushi domain polypeptide and the IL-15 polypeptide are fused to (ii) the N-terminus of the heavy chain variable region, optionally by a second linker.

91. The fusion protein of claim **90**, wherein the first linker (i) is between 5 and 40 amino acids long, optionally, consists predominantly of Gly (G), Asn (N), Ser (S), Thr (T), Ala (A), Leu (L), and Gln (Q); and/or (ii) comprises a sequence selected from the group consisting of SEQ ID NOS: 215-218 and 244.

92. The fusion protein of claim **91**, wherein the second linker (i) is between 5 and 40 amino acids long, optionally, consists predominantly of Gly (G), Asn (N), Ser (S), Thr (T), Ala (A), Leu (L), and Gln (Q), and/or (ii) comprises a sequence selected from the group consisting of SEQ ID NOS: 215-218 and 244.

93. The fusion protein of claim **92**, wherein the fusion protein comprises not more than one IL-15Rα sushi domain polypeptide and not more than one IL-15 polypeptide.

94. The fusion protein of claim **92**, wherein the IL-15 polypeptide is a mutant IL-15 polypeptide comprising one or more amino acid substitutions at positions 45, 65, or 108 as numbered according to the mature human IL-15 sequence of SEQ ID NO: 212, wherein the one or more amino acid substitutions in the IL-15 polypeptide are selected from L45A, N65A, N65D, N65S, N65K, and Q108S as numbered according to the mature human IL-15 sequence of SEQ ID NO: 212.

95. A fusion protein comprising a light chain sequence comprising SEQ ID NO: 219 or SEQ ID NO: 98 and a first heavy chain sequence comprising SEQ ID NO: 240 and a second heavy chain sequence comprising SEQ ID NO: 241.

96. A nucleic acid sequence encoding the anti-PD-1 antibody, or an antigen-binding fragment thereof of claim **77**.

97. A cell comprising the nucleic acid of claim **96**.

98. A vector comprising nucleic acids encoding the light and heavy chains encoding the anti-PD-1 antibody, or an antigen-binding fragment thereof, of claim **77**.

99. A pharmaceutical composition comprising (i) the anti-PD-1 antibody, or an antigen-binding fragment thereof, of claim **77**; and (ii) a pharmaceutically acceptable carrier.

100. A method of inhibiting binding of PD-1 to a ligand of PD-1, optionally PD-L1 or PD-L2, in a subject in need

thereof, the method comprising administering to the subject an effective amount of the anti-PD-1 antibody, or an antigen-binding fragment thereof, of claim **77**.

101. A method for increasing T cell activation or stimulating the immune system in a subject in need thereof, the method comprising administering to the subject an effective amount of the anti-PD-1 antibody, or an antigen-binding fragment thereof, of claim **77**.

102. A method of treating cancer or reducing tumor growth or tumor metastasis in a subject in need thereof, the method comprising administering to the subject an effective amount of the anti-PD-1 antibody, or an antigen-binding fragment thereof, of claim **77**.

103. A method of inhibiting binding of PD-1 to a ligand of PD-1, optionally PD-L1 or PD-L2, in a subject in need thereof, the method comprising administering to the subject an effective amount of the fusion protein of claim **89**.

104. A method for increasing T cell activation or stimulating the immune system in a subject in need thereof, the method comprising administering to the subject an effective amount of the fusion protein of claim **89**.

105. A method of treating cancer or reducing tumor growth or tumor metastasis in a subject in need thereof, the method comprising administering to the subject an effective amount of fusion protein of claim **89**.

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