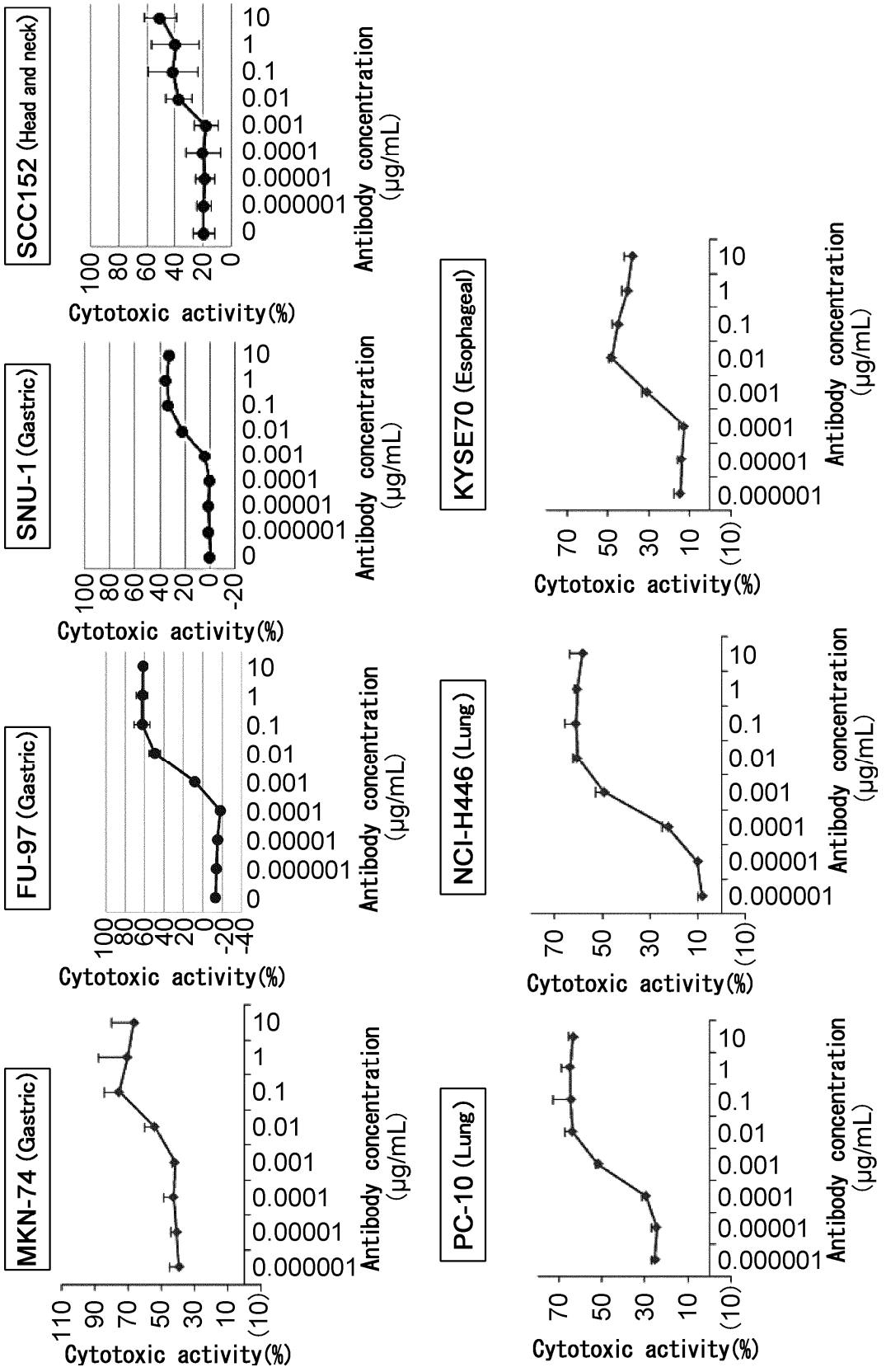

SCC152 (Head and neck)
SNU-1 (Gastric)
FU-97 (Gastric)
MKN-74 (Gastric)
KYSE70 (Esophageal)
NCI-H446 (Lung)
PC-10 (Lung)
Cytotoxic activity(%)
Antibody concentration (μg/mL)
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
0

FIG. 1-1

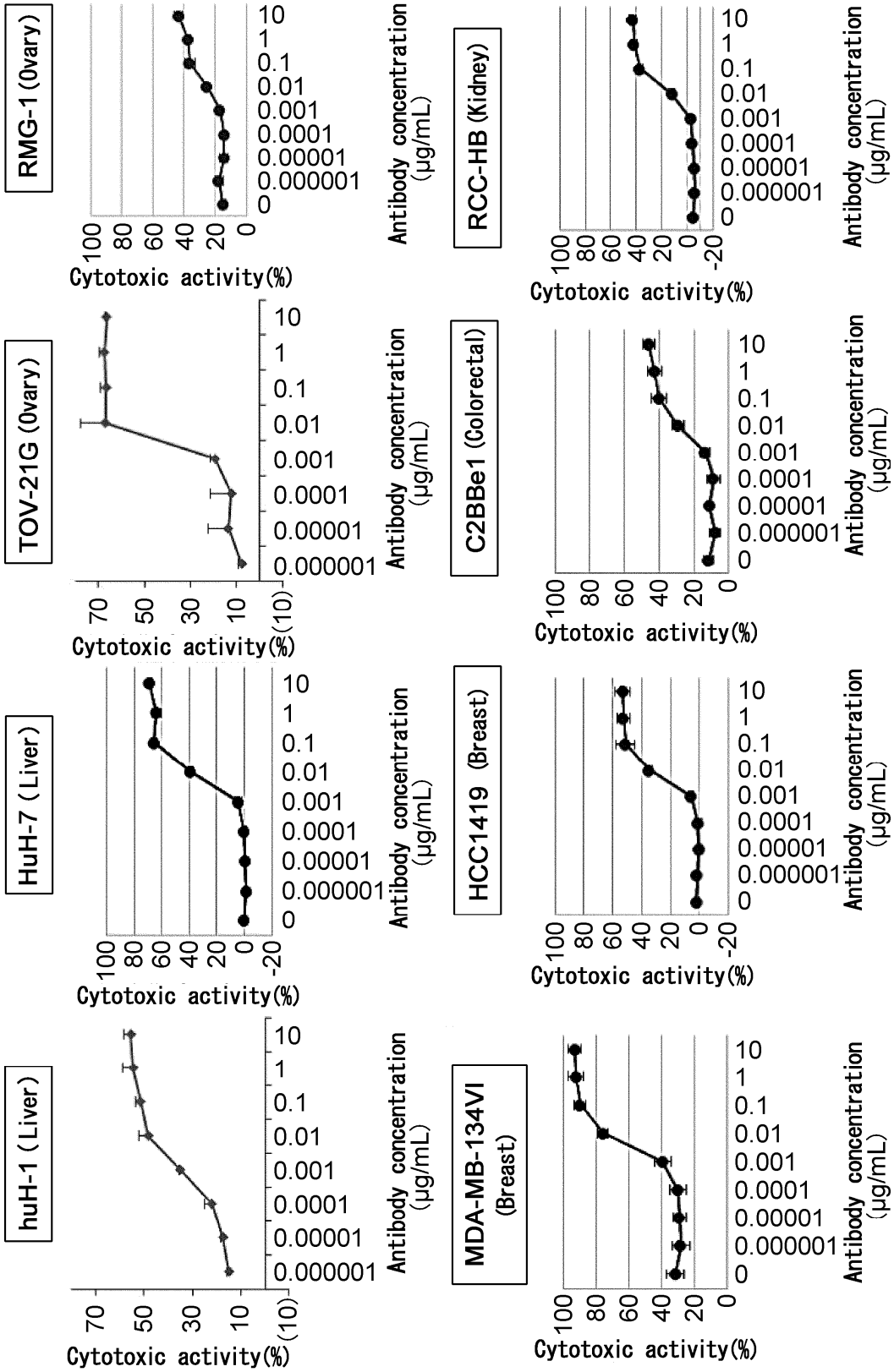

RMG-1 (Ovary)
TOV-21G (Ovary)
HuH-7 (Liver)
huH-1 (Liver)
RCC-HB (Kidney)
C2BBe1 (Colorectal)
HCC1419 (Breast)
MDA-MB-134VI (Breast)
Cytotoxic activity(%)
Antibody concentration (μg/mL)
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
0

FIG. 1-2

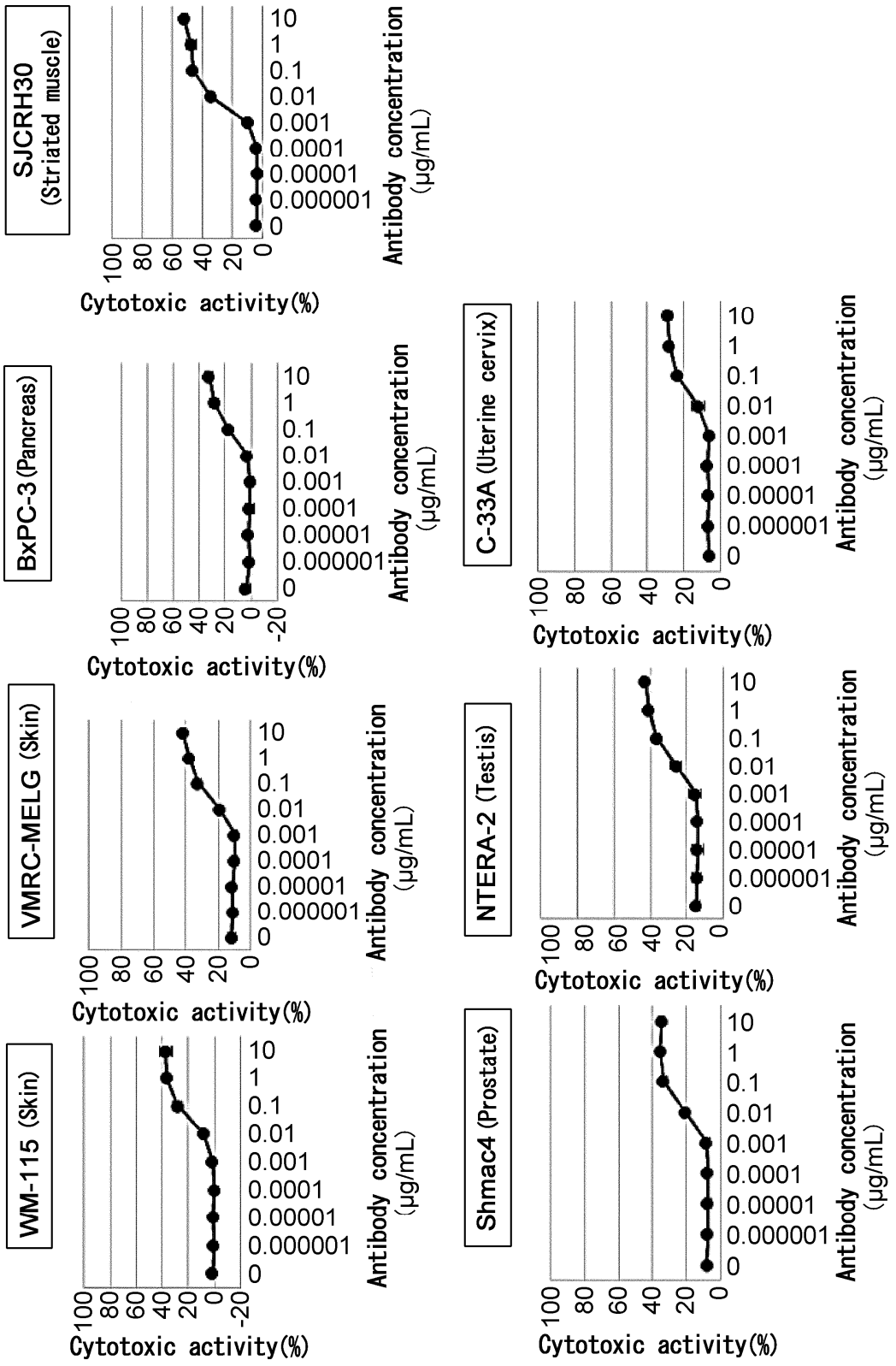

SJCRH30 (Striated muscle)
BxPC-3 (Pancreas)
C-33A (Uterine cervix)
VMRC-MELG (Skin)
NTERA-2 (Testis)
WM-115 (Skin)
Shmac4 (Prostate)
Cytotoxic activity(%)
Antibody concentration (μg/mL)
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
0
100
80
60
40
20
0
-20

FIG. 1-3

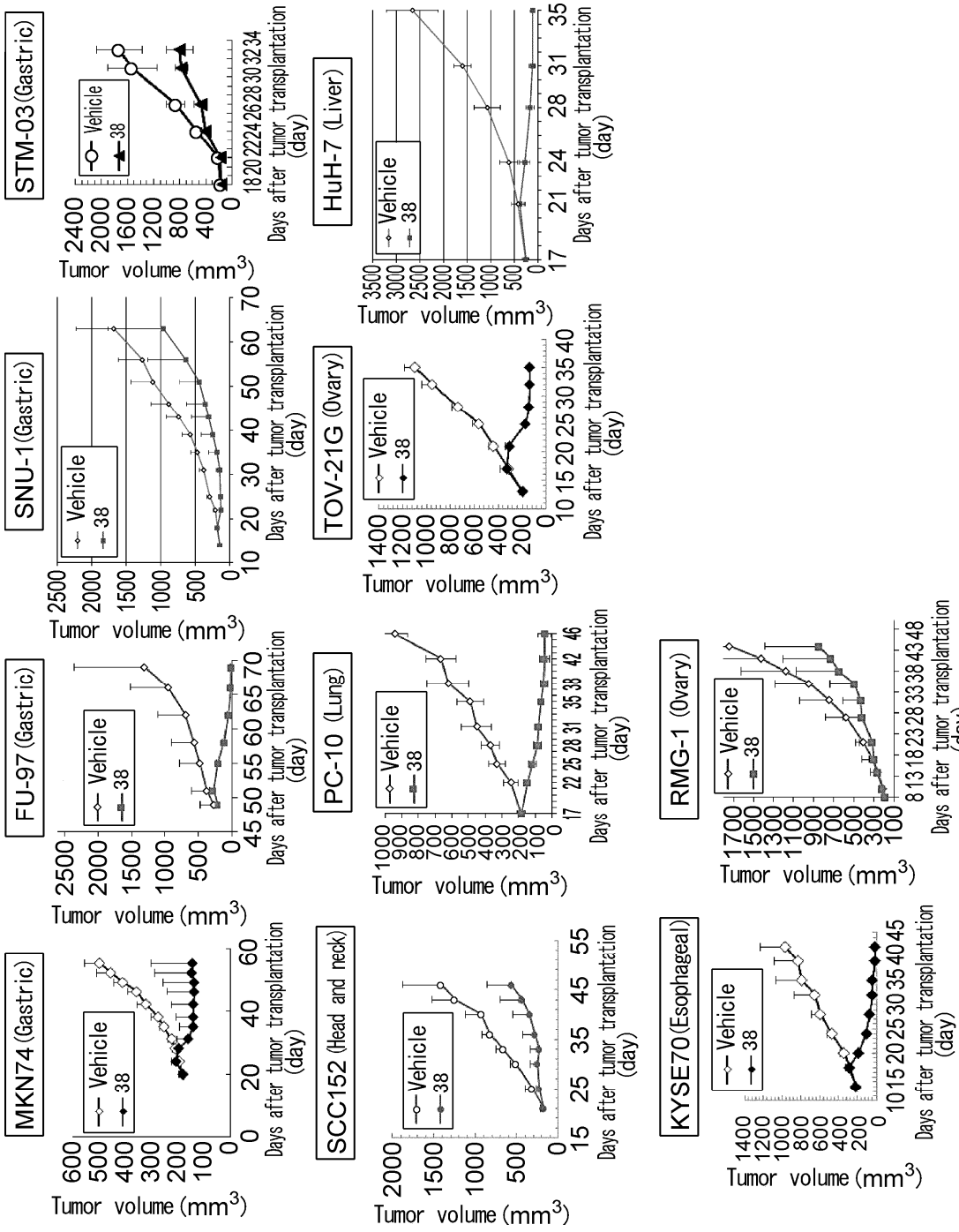

STM-03 (Gastric)
HuH-7 (Liver)
SNU-1 (Gastric)
TOV-21G (Ovary)
FU-97 (Gastric)
PC-10 (Lung)
MKN74 (Gastric)
SCC152 (Head and neck)
RMG-1 (Ovary)
KYSE70 (Esophageal)
Vehicle
38
Tumor volume (mm3)
Days after tumor transplantation (day)

FIG. 2

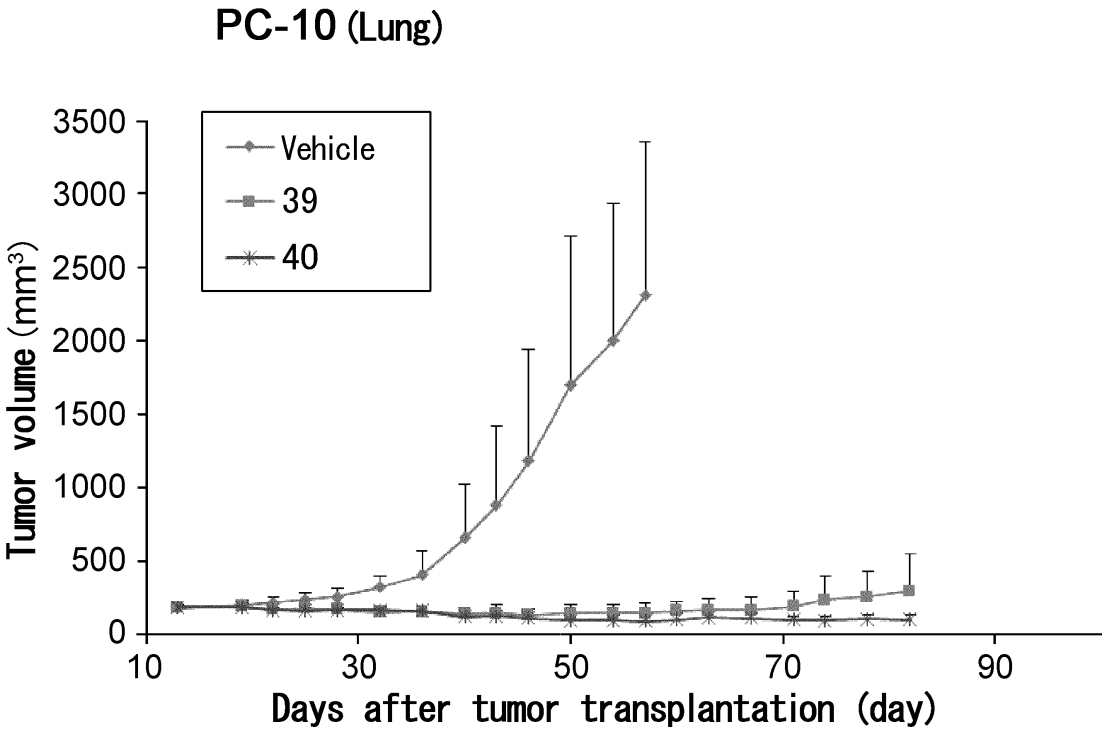

PC-10 (Lung)
Vehicle
39
40
Tumor volume (mm3)
3500
3000
2500
2000
1500
1000
500
0
10
30
50
70
90
Days after tumor transplantation (day)

FIG. 3

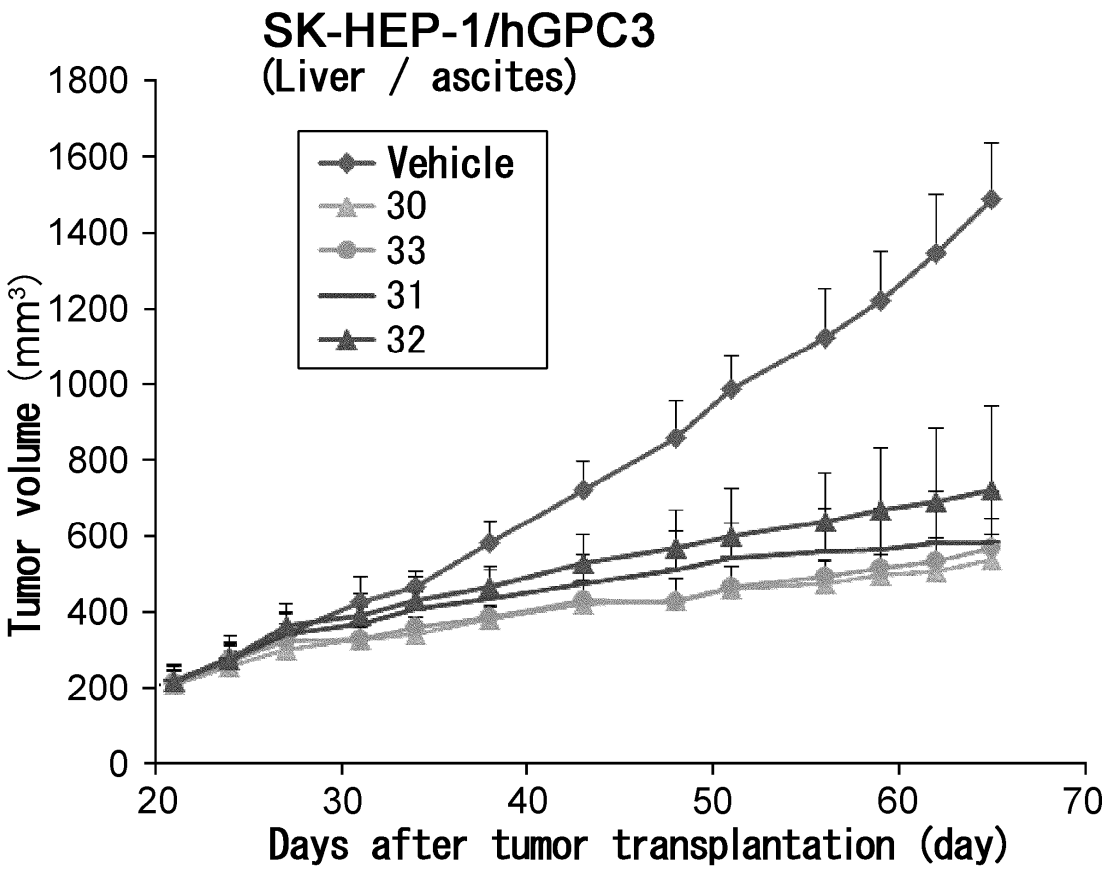

SK-HEP-1/hGPC3
(Liver / ascites)
Vehicle
30
33
31
32
Tumor volume (mm3)
1800
1600
1400
1200
1000
800
600
400
200
0
20
30
40
50
60
70
Days after tumor transplantation (day)

FIG. 4

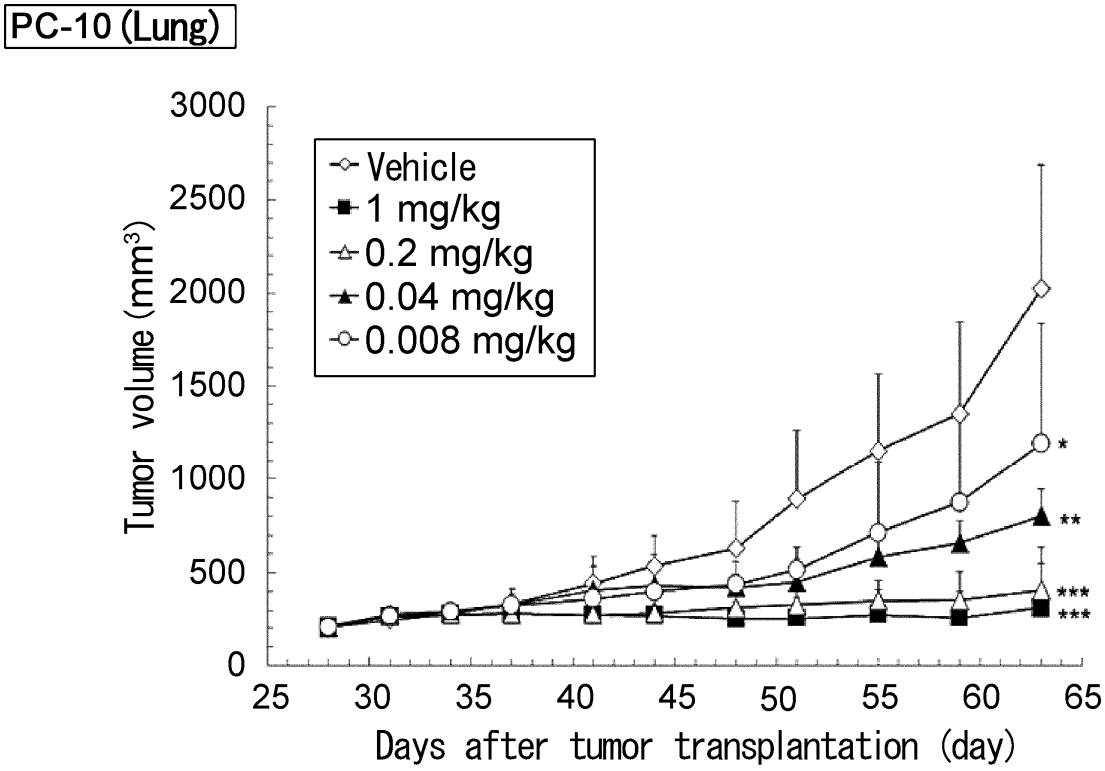

PC-10 (Lung)
Tumor volume (mm3)
3000
2500
2000
1500
1000
500
0
25
30
35
40
45
50
55
60
65
Days after tumor transplantation (day)
Vehicle
1 mg/kg
0.2 mg/kg
0.04 mg/kg
0.008 mg/kg
*
**
***
***

FIG. 5

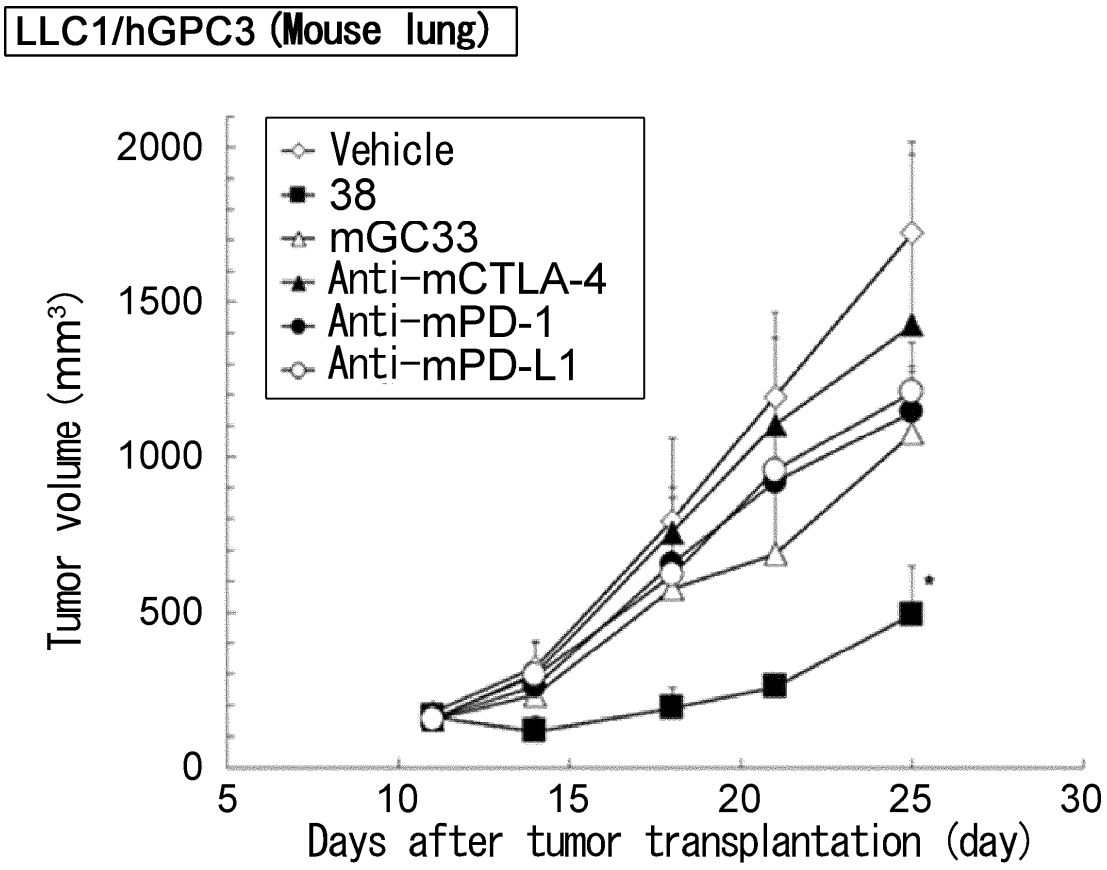

LLC1/hGPC3 (Mouse lung)
Vehicle
38
mGC33
Anti-mCTLA-4
Anti-mPD-1
Anti-mPD-L1
Tumor volume (mm3)
2000
1500
1000
500
0
5
10
15
20
25
30
Days after tumor transplantation (day)
*

FIG. 6

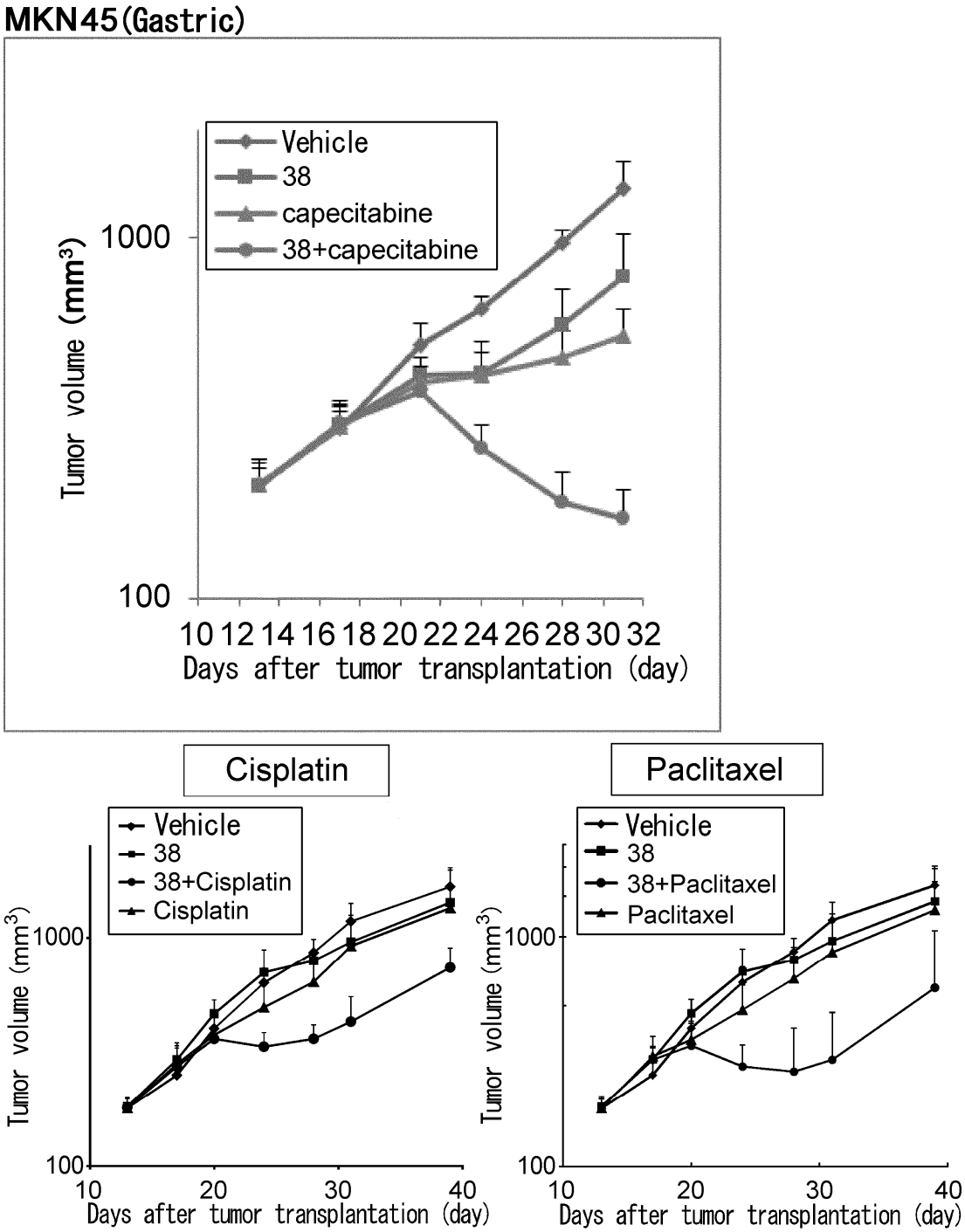

MKN45(Gastric)
Vehicle
38
capecitabine
38+capecitabine
Tumor volume (mm3)
1000
100
10 12 14 16 18 20 22 24 26 28 30 32
Days after tumor transplantation (day)
Cisplatin
Vehicle
38
38+Cisplatin
Cisplatin
Tumor volume (mm3)
1000
100
10
20
30
40
Days after tumor transplantation (day)
Paclitaxel
Vehicle
38
38+Paclitaxel
Paclitaxel
Tumor volume (mm3)
1000
100
10
20
30
40
Days after tumor transplantation (day)

FIG. 7

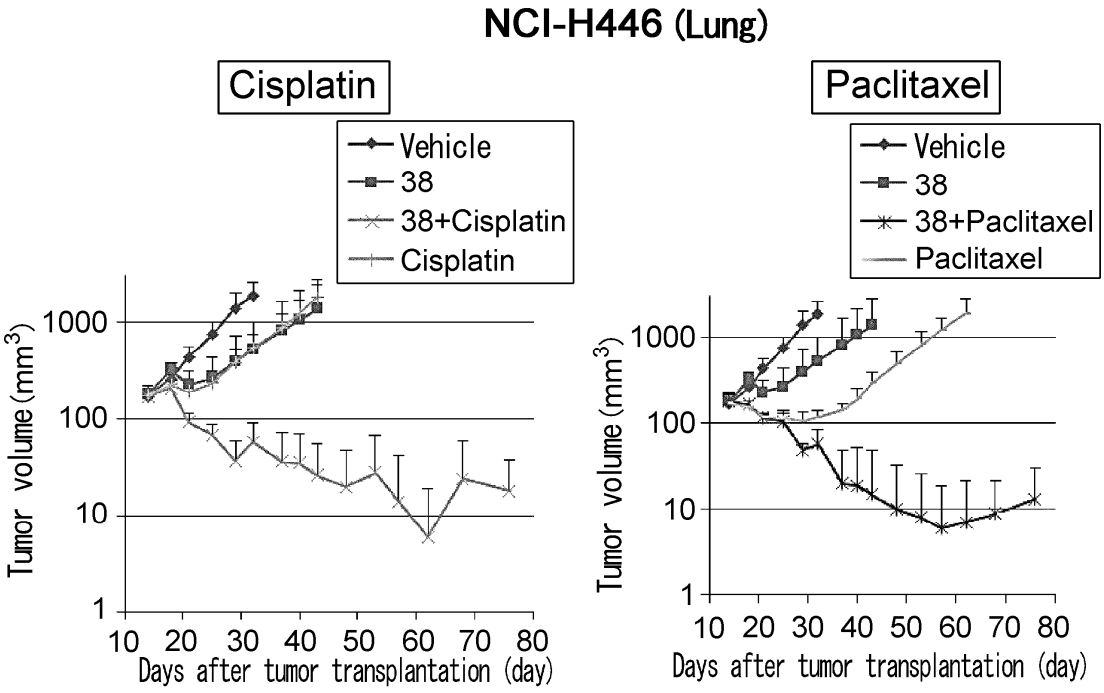

NCI-H446 (Lung)
Cisplatin
Vehicle
38
38+Cisplatin
Cisplatin
Tumor volume (mm3)
1000
100
10
1
10 20 30 40 50 60 70 80
Days after tumor transplantation (day)
Paclitaxel
Vehicle
38
38+Paclitaxel
Paclitaxel
Tumor volume (mm3)
1000
100
10
1
10 20 30 40 50 60 70 80
Days after tumor transplantation (day)

FIG. 8

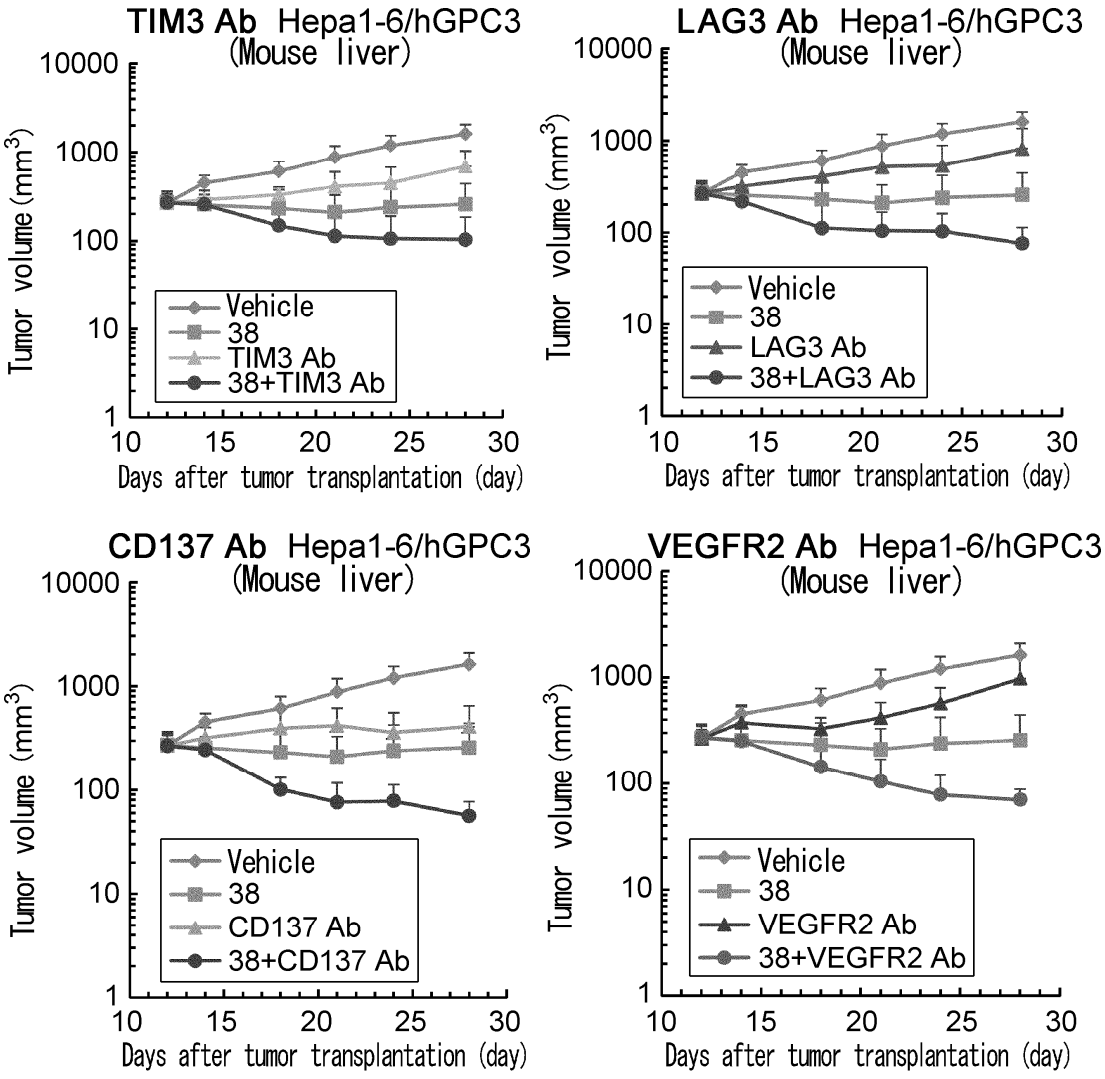

TIM3 Ab Hepa1-6/hGPC3
(Mouse liver)
Tumor volume (mm3)
10000
1000
100
10
1
10
15
20
25
30
Days after tumor transplantation (day)
Vehicle
38
TIM3 Ab
38+TIM3 Ab
LAG3 Ab Hepa1-6/hGPC3
(Mouse liver)
Tumor volume (mm3)
Days after tumor transplantation (day)
Vehicle
38
LAG3 Ab
38+LAG3 Ab
CD137 Ab Hepa1-6/hGPC3
(Mouse liver)
Tumor volume (mm3)
Days after tumor transplantation (day)
Vehicle
38
CD137 Ab
38+CD137 Ab
VEGFR2 Ab Hepa1-6/hGPC3
(Mouse liver)
Tumor volume (mm3)
Days after tumor transplantation (day)
Vehicle
38
VEGFR2 Ab
38+VEGFR2 Ab

FIG. 9

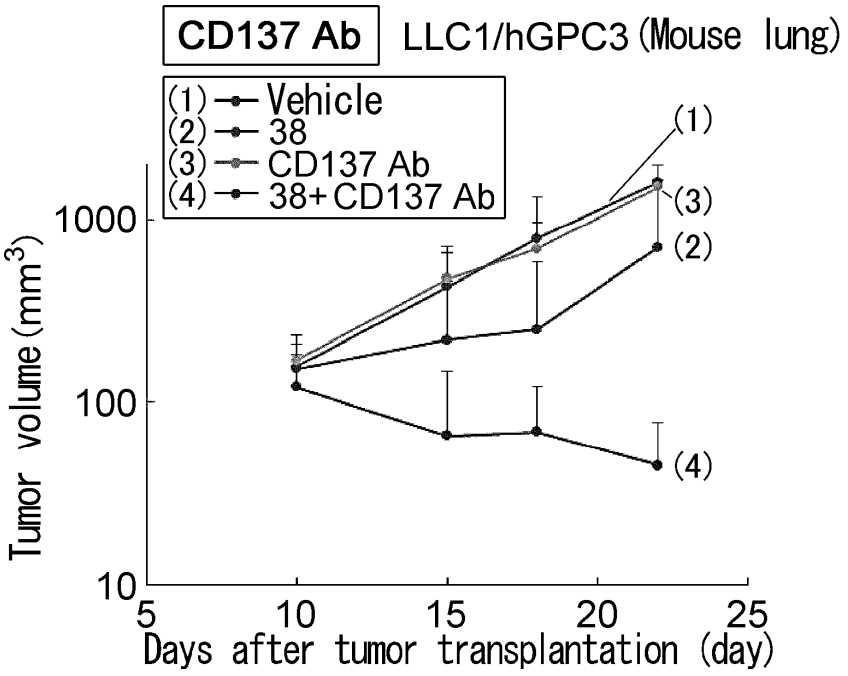

CD137 Ab
LLC1/hGPC3 (Mouse lung)
(1) Vehicle
(2) 38
(3) CD137 Ab
(4) 38+CD137 Ab
Tumor volume (mm3)
1000
100
10
5
10
15
20
25
Days after tumor transplantation (day)
(1)
(3)
(2)
(4)

FIG. 10

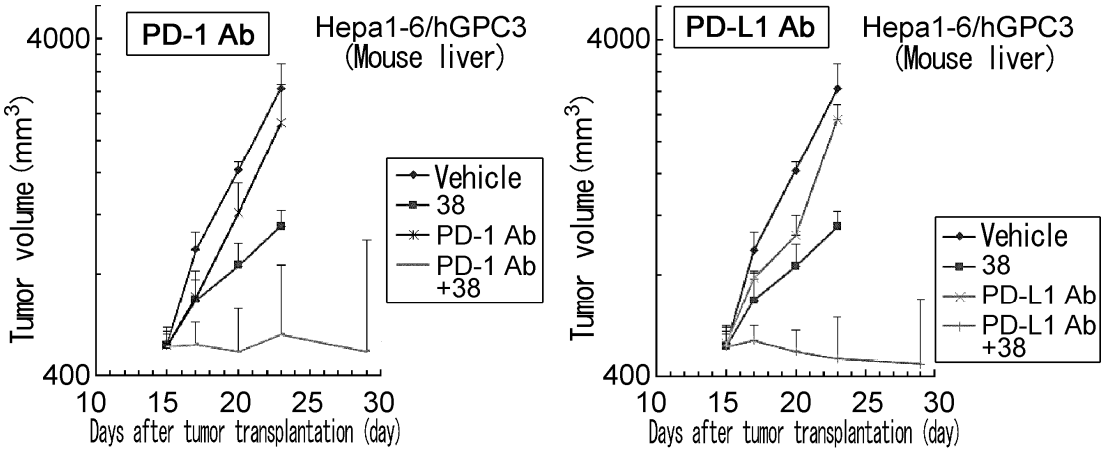
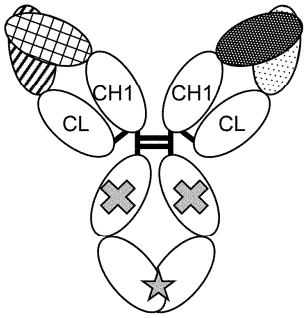
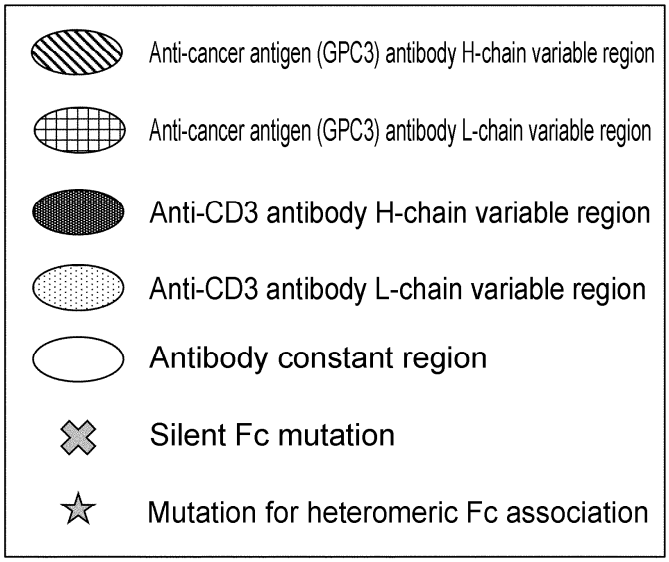

PD-1 Ab
Hepa1-6/hGPC3
(Mouse liver)
Tumor volume (mm3)
4000
400
10
15
20
25
30
Days after tumor transplantation (day)
Vehicle
38
PD-1 Ab
PD-1 Ab +38
PD-L1 Ab
Hepa1-6/hGPC3
(Mouse liver)
Tumor volume (mm3)
4000
400
10
15
20
25
30
Days after tumor transplantation (day)
Vehicle
38
PD-L1 Ab
PD-L1 Ab +38

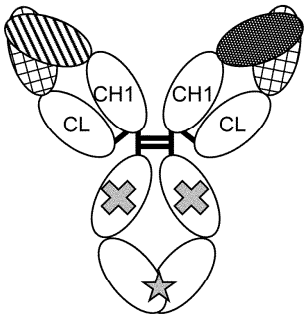
FIG. 11

a ERY22





b ERY27



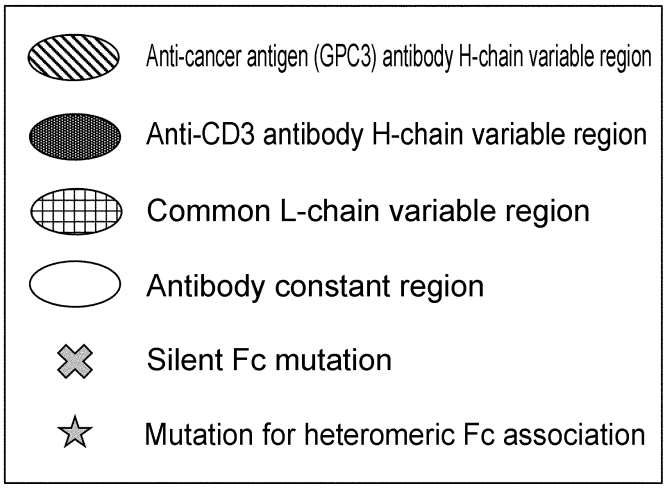


FIG. 12

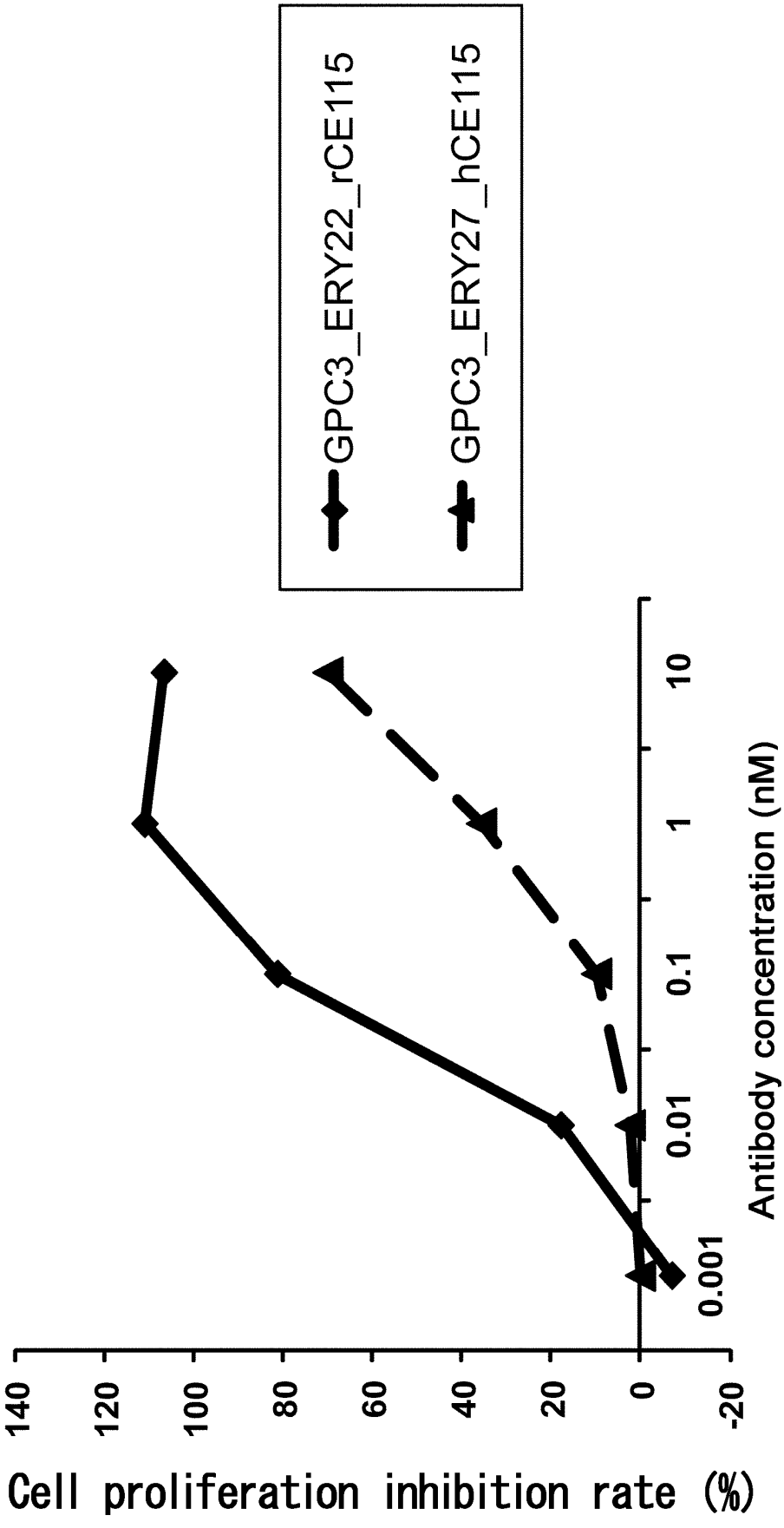

GPC3_ERY22_rCE115
GPC3_ERY27_hCE115
Cell proliferation inhibition rate (%)
140
120
100
80
60
40
20
0
-20
0.001
0.01
0.1
1
10
Antibody concentration (nM)

FIG. 13

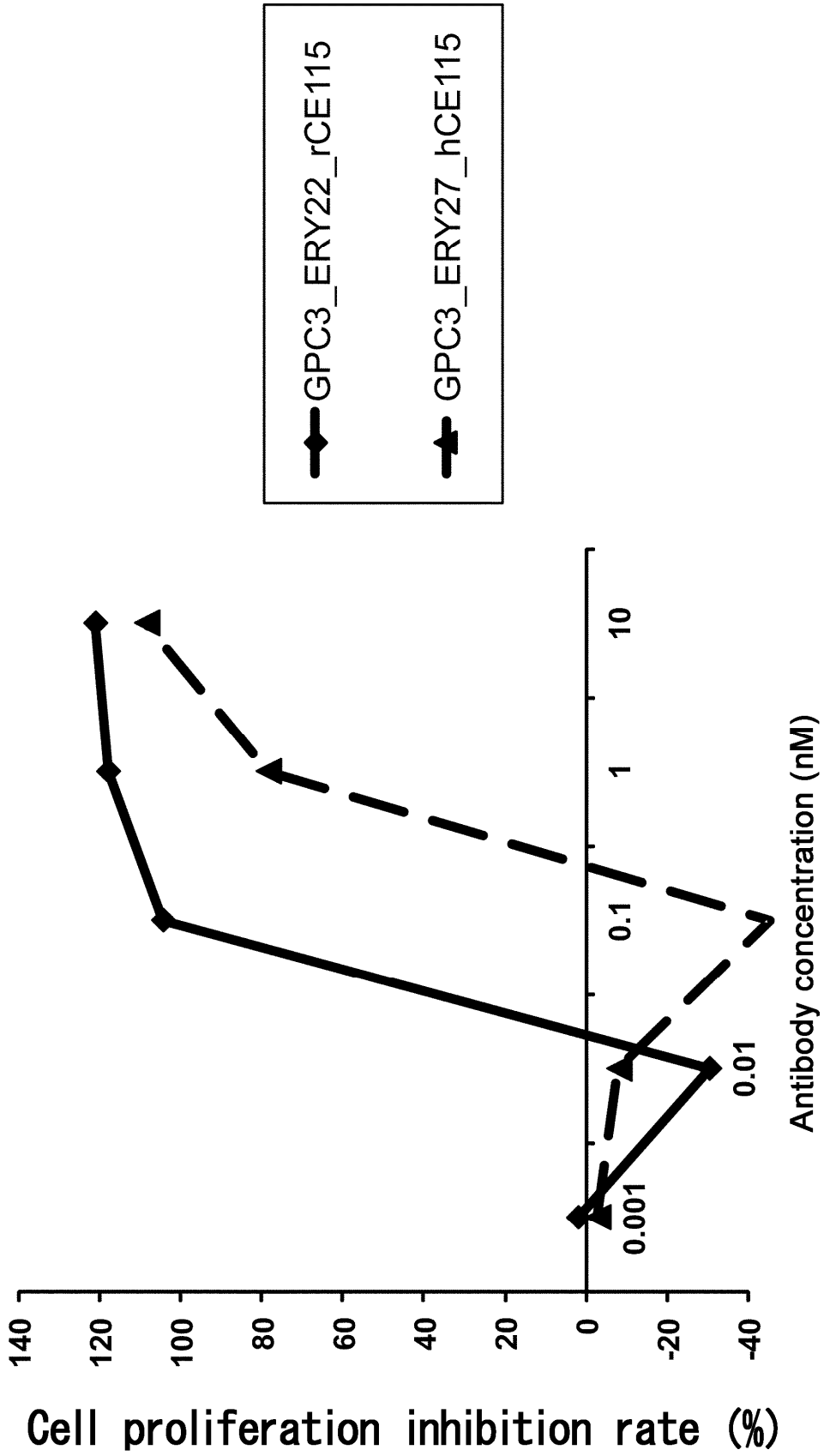

GPC3_ERY22_rCE115
GPC3_ERY27_hCE115
Cell proliferation inhibition rate (%)
140
120
100
80
60
40
20
0
-20
-40
0.001
0.01
0.1
1
10
Antibody concentration (nM)

FIG. 14

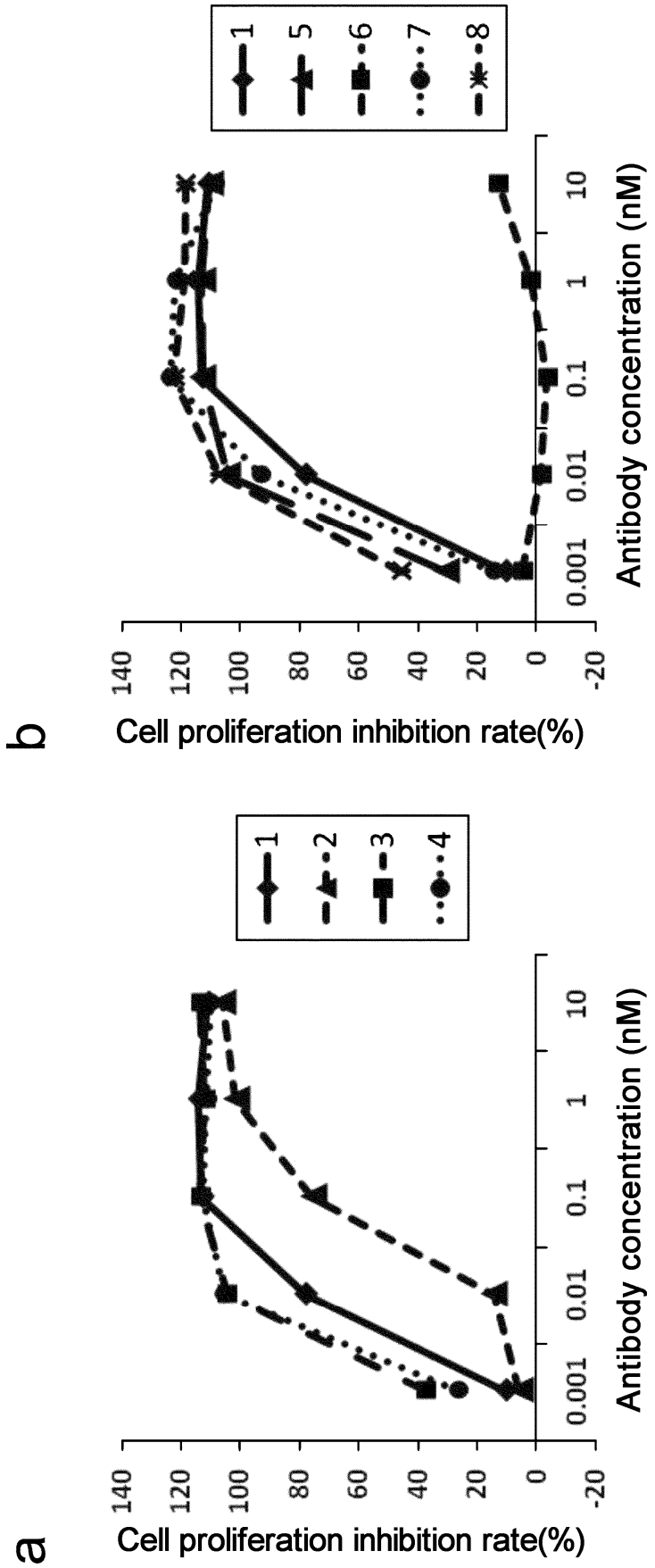

a
Cell proliferation inhibition rate(%)
140
120
100
80
60
40
20
0
-20
0.001
0.01
0.1
1
10
Antibody concentration (nM)
1
2
3
4
b
Cell proliferation inhibition rate(%)
140
120
100
80
60
40
20
0
-20
0.001
0.01
0.1
1
10
Antibody concentration (nM)
1
5
6
7
8

FIG. 15

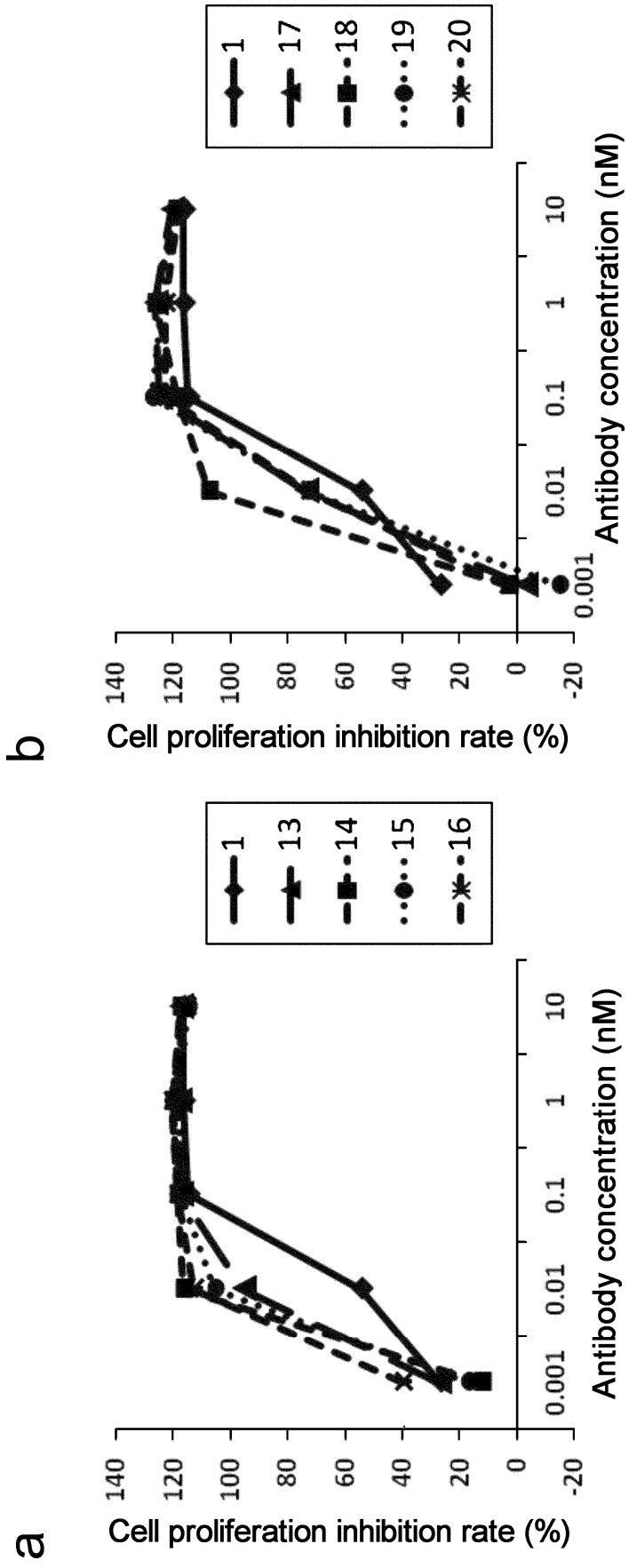

a
b
Cell proliferation inhibition rate (%)
Antibody concentration (nM)
140
120
100
80
60
40
20
0
-20
0.001
0.01
0.1
1
10
1
13
14
15
16
17
18
19
20

FIG. 16

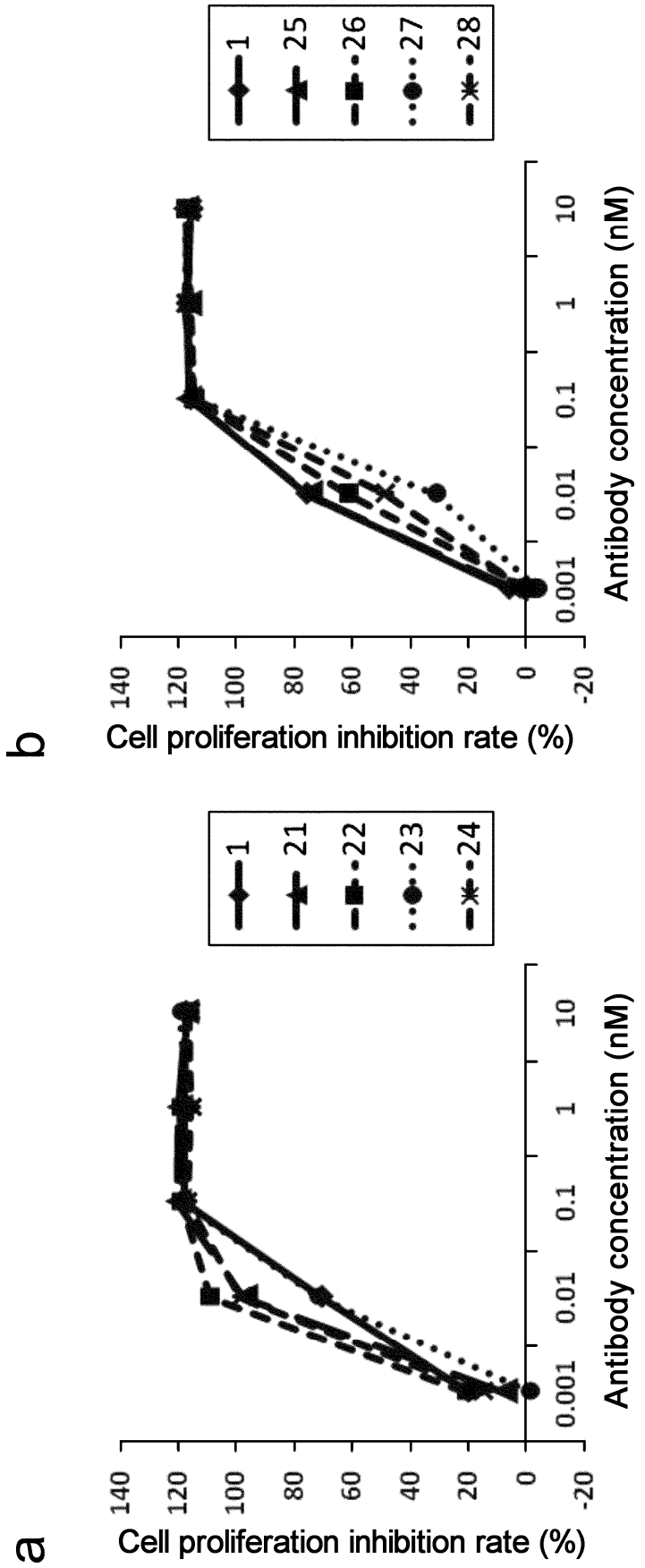

a
Cell proliferation inhibition rate (%)
140
120
100
80
60
40
20
0
-20
0.001
0.01
0.1
1
10
Antibody concentration (nM)
1
21
22
23
24
b
Cell proliferation inhibition rate (%)
140
120
100
80
60
40
20
0
-20
0.001
0.01
0.1
1
10
Antibody concentration (nM)
1
25
26
27
28

FIG. 17

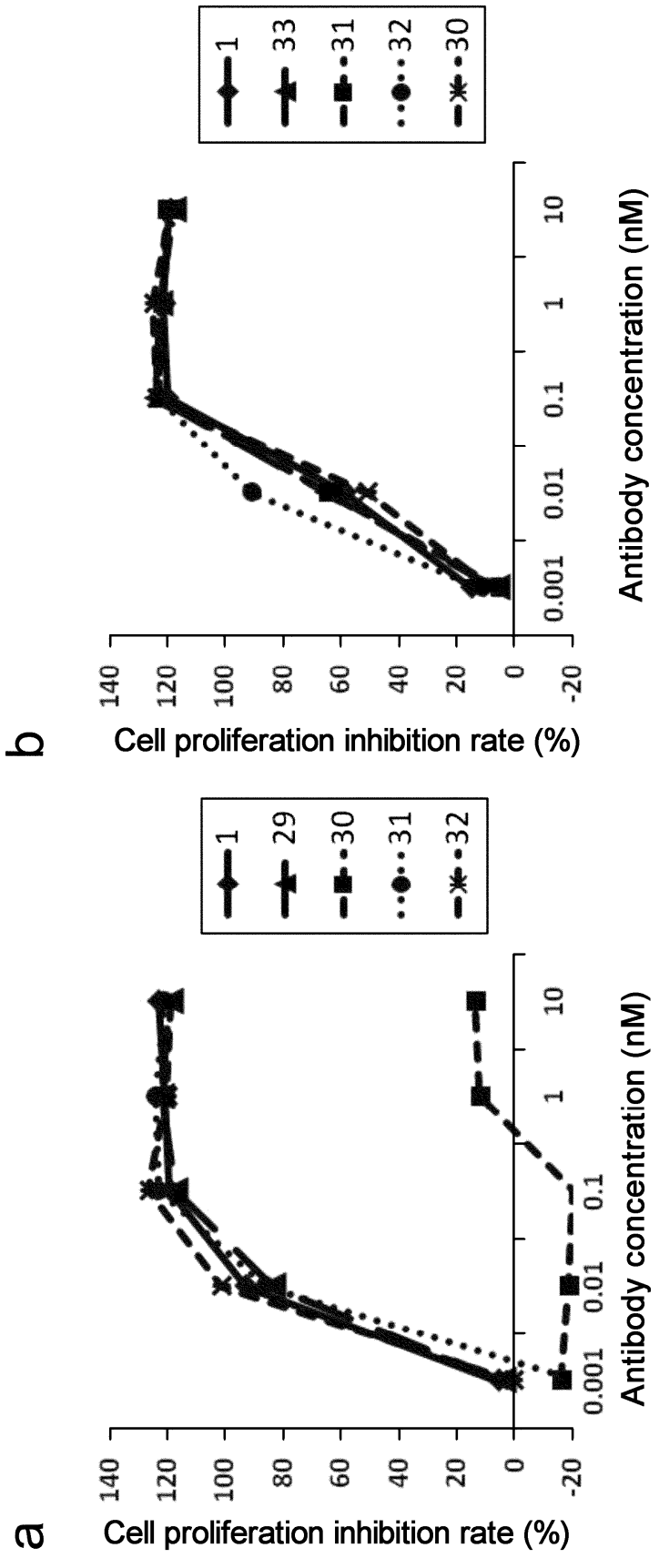

a
Cell proliferation inhibition rate (%)
140
120
100
80
60
40
20
0
-20
0.001
0.01
0.1
1
10
Antibody concentration (nM)
1
29
30
31
32
b
Cell proliferation inhibition rate (%)
140
120
100
80
60
40
20
0
-20
0.001
0.01
0.1
1
10
Antibody concentration (nM)
1
33
31
32
30

FIG. 18

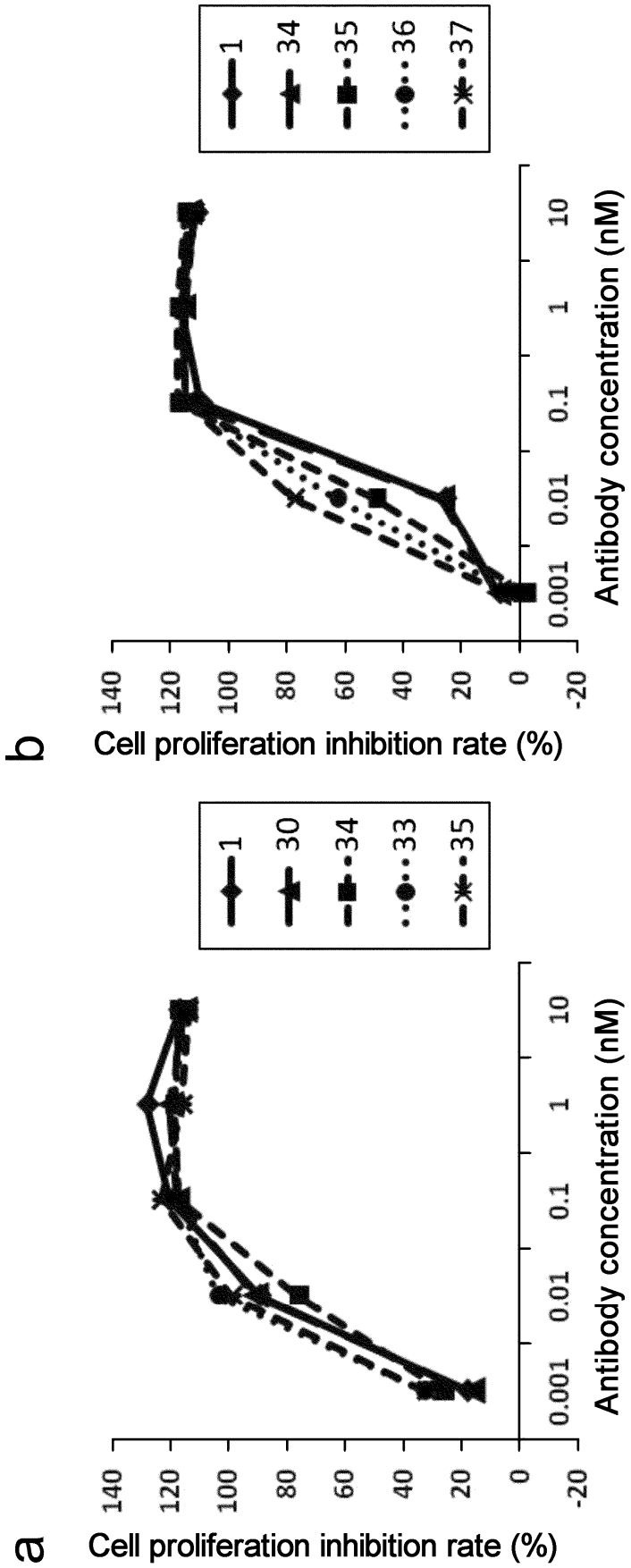

a
Cell proliferation inhibition rate (%)
140
120
100
80
60
40
20
0
-20
0.001
0.01
0.1
1
10
Antibody concentration (nM)
1
30
34
33
35
b
Cell proliferation inhibition rate (%)
140
120
100
80
60
40
20
0
-20
0.001
0.01
0.1
1
10
Antibody concentration (nM)
1
34
35
36
37

FIG. 19

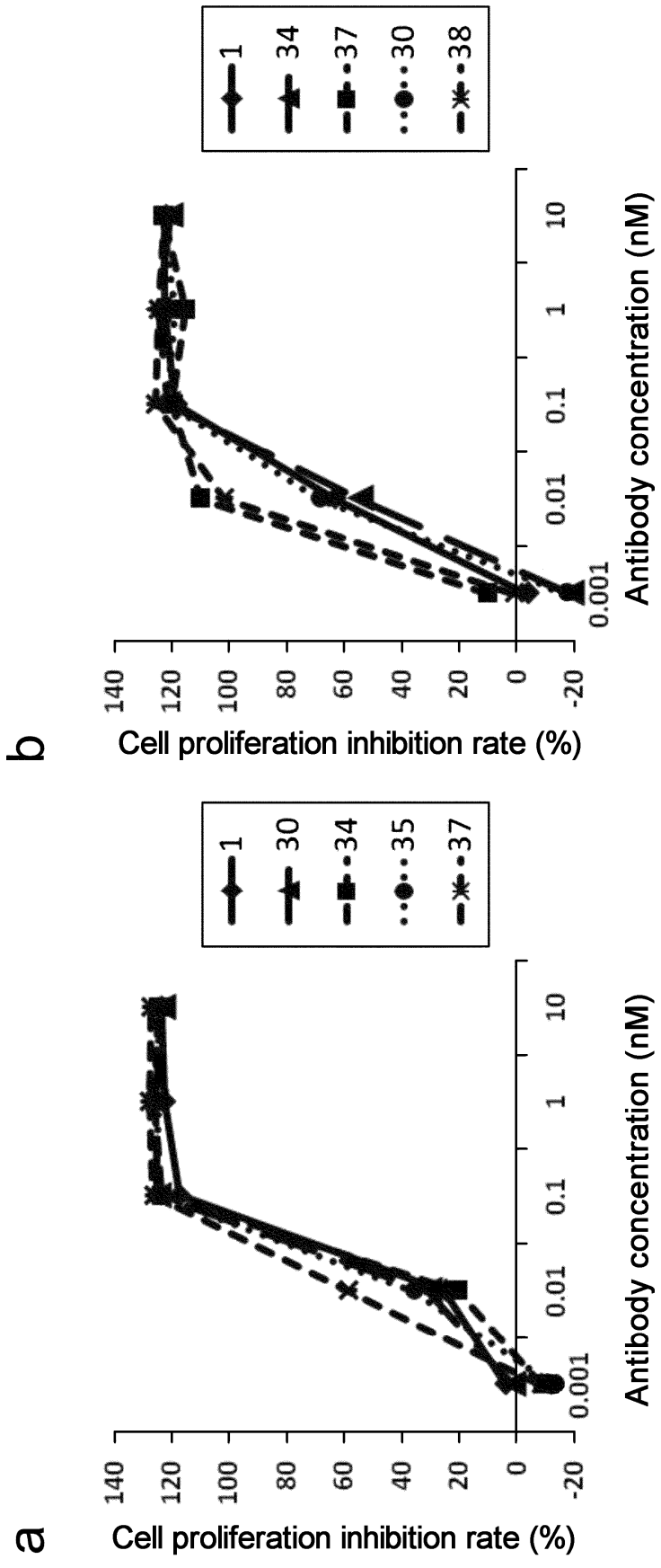

a
Cell proliferation inhibition rate (%)
140
120
100
80
60
40
20
0
-20
0.001
0.01
0.1
1
10
Antibody concentration (nM)
1
30
34
35
37
b
Cell proliferation inhibition rate (%)
140
120
100
80
60
40
20
0
-20
0.001
0.01
0.1
1
10
Antibody concentration (nM)
1
34
37
30
38

FIG. 20

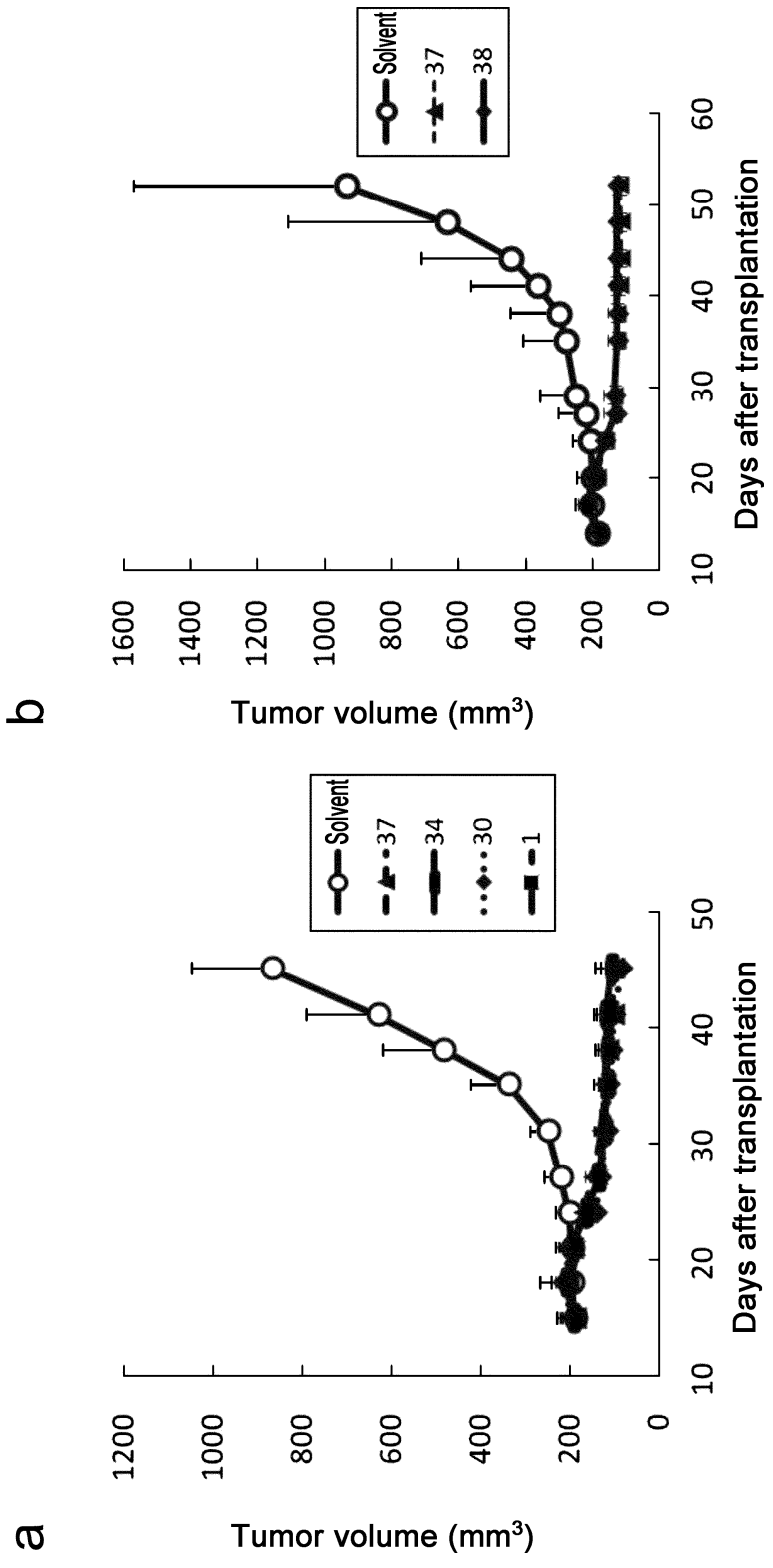

a
Tumor volume (mm3)
1200
1000
800
600
400
200
0
10
20
30
40
50
Days after transplantation
Solvent
37
34
30
1
b
Tumor volume (mm3)
1600
1400
1200
1000
800
600
400
200
0
10
20
30
40
50
60
Days after transplantation
Solvent
37
38

FIG. 21

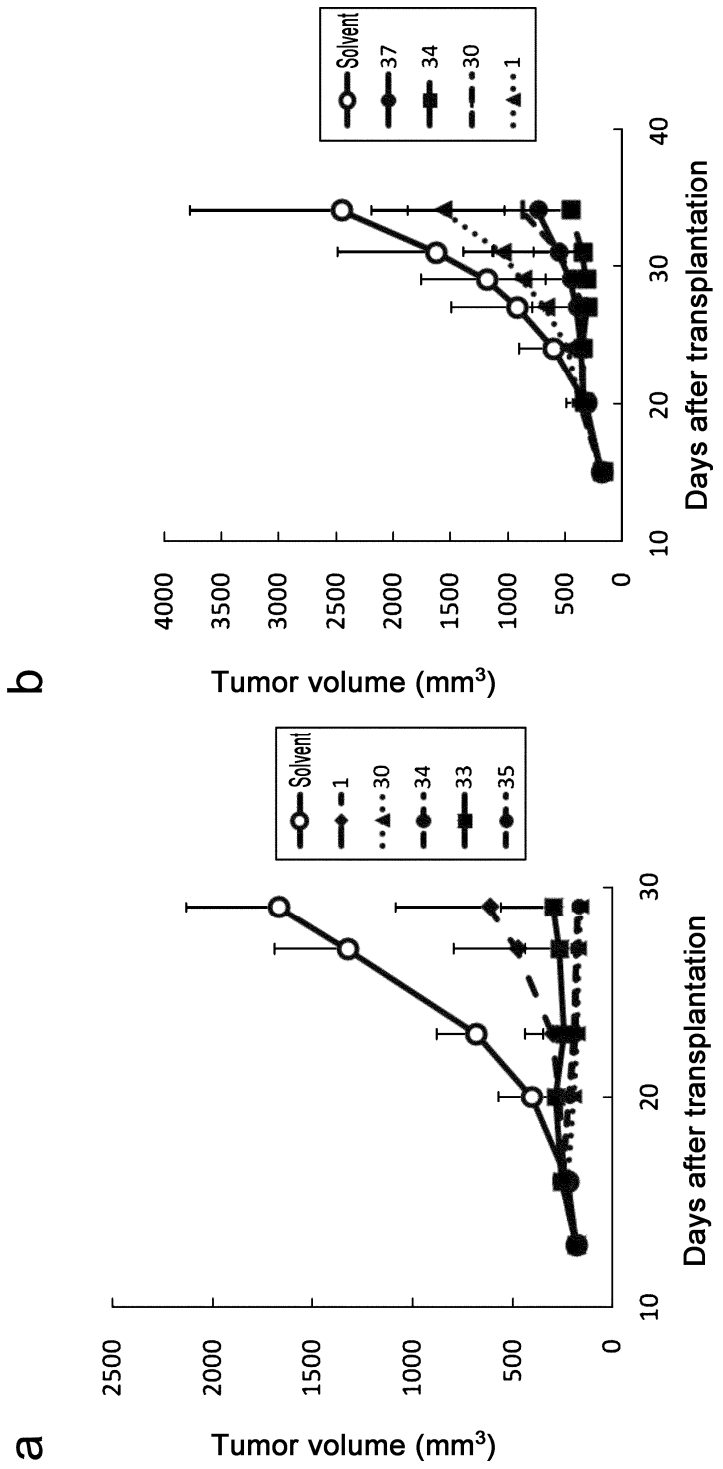

a
Tumor volume (mm3)
2500
2000
1500
1000
500
0
10
20
30
Days after transplantation
Solvent
1
30
34
33
35
b
Tumor volume (mm3)
4000
3500
3000
2500
2000
1500
1000
500
0
10
20
30
40
Days after transplantation
Solvent
37
34
30
1

FIG. 22

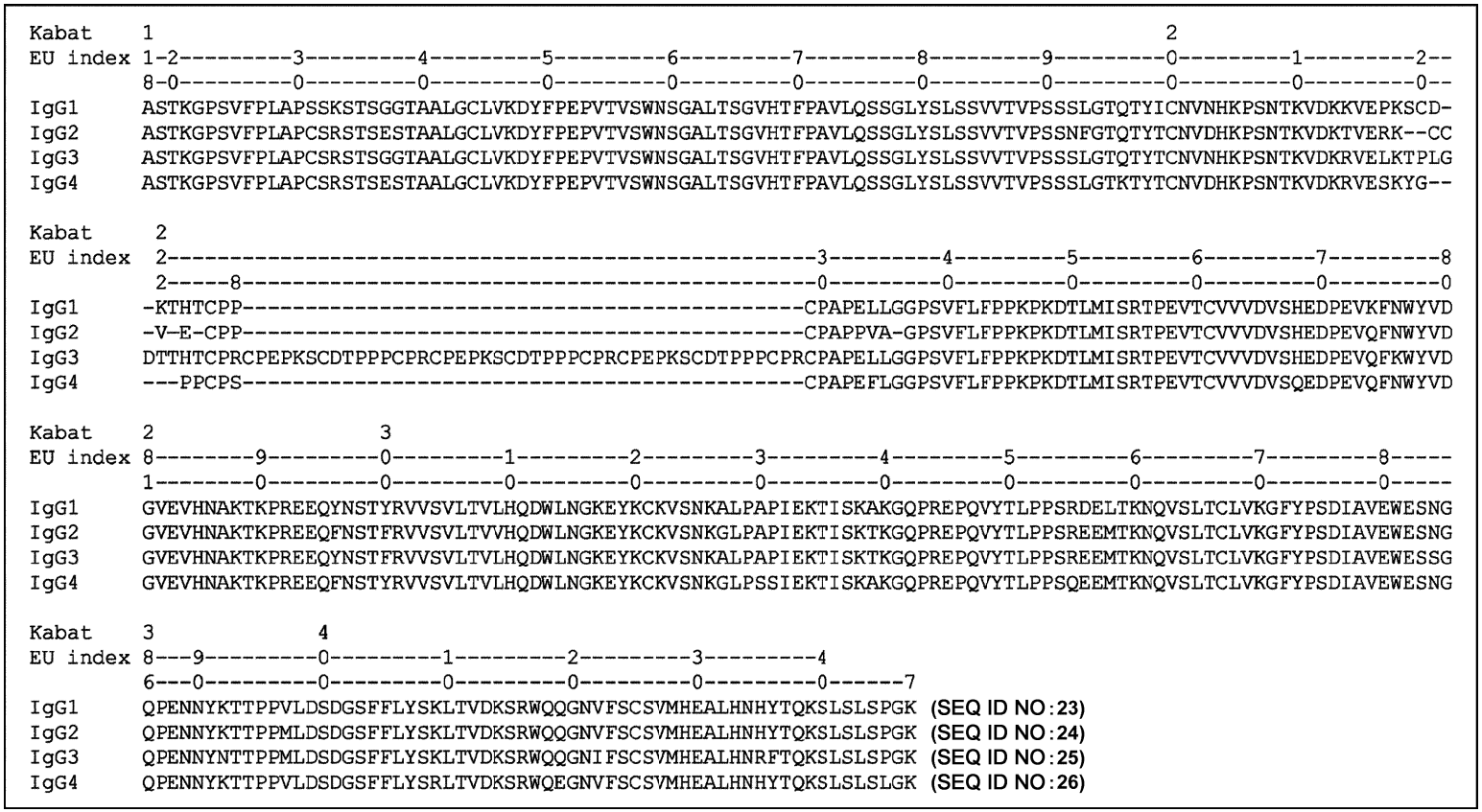

Kabat 1 2
EU index 1-2---------3---------4---------5---------6---------7---------8---------9---------0---------1---------2--
8-0---------0---------0---------0---------0---------0---------0---------0---------0---------0---------0--
IgG1 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD-
IgG2 ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERK--CC
IgG3 ASTKGPSVFPLAPCSRSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVNHKPSNTKVDKRVELKTPLG
IgG4 ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYG--
Kabat 2
EU index 2----------3---------4---------5---------6---------7---------8
2-----8---------0---------0---------0---------0---------0---------0
IgG1 -KTHTCPP----------CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
IgG2 -V-E-CPP----------CPAPPVA-GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVD
IgG3 DTTHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFKWYVD
IgG4 ---PPCPS----------CPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD
Kabat 2 3
EU index 8--------9---------0---------1---------2---------3---------4---------5---------6---------7---------8-----
1--------0---------0---------0---------0---------0---------0---------0---------0---------0---------0-----
IgG1 GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNG
IgG2 GVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG
IgG3 GVEVHNAKTKPREEQYNSTFRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESSG
IgG4 GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNG
Kabat 3 4
EU index 8---9---------0---------1---------2---------3---------4
6---0---------0---------0---------0---------0---------0------7
IgG1 QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:23)
IgG2 QPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:24)
IgG3 QPENNYNTTPPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK (SEQ ID NO:25)
IgG4 QPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO:26)

FIG. 23

Kabat CDR H1: positions 31–35b; Chothia CDR H1: positions 26–32; Contact CDR H1: positions 30–35

Antibody name	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	35a	35b	36	37	38	39	40
CE115HA000	Q	V	Q	L	V	E	S	G	G	G	V	V	Q	P	G	R	S	L	R	L	S	C	A	A	S	G	F	T	F	S	N	A	W	M	H	-	-	W	V	R	Q	A
TR01H040	Q	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	R	S	L	R	L	S	C	A	A	S	G	F	T	F	S	N	A	W	M	H	-	-	W	V	R	Q	A
TR01H071	Q	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	R	S	L	R	L	S	C	A	A	S	G	F	T	F	S	N	A	W	M	H	-	-	W	V	R	Q	A
TR01H082	Q	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	R	S	L	R	L	S	C	A	A	S	G	F	T	F	S	N	A	W	M	H	-	-	W	V	R	Q	A
TR01H084	Q	V	Q	L	V	E	S	G	G	G	V	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	S	N	A	W	M	H	-	-	W	V	R	Q	A
TR01H109	Q	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	R	S	L	R	L	S	C	A	A	S	G	F	T	F	S	N	A	W	M	H	-	-	W	V	R	Q	A
TR01H113	Q	V	Q	L	V	E	S	G	G	G	V	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	S	N	A	W	M	H	-	-	W	V	R	Q	A
H0000	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	D	Y	E	M	H	-	-	W	I	R	Q	P
H0610	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	D	Y	E	M	H	-	-	W	I	R	Q	P
GCH054	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	T	V	S	C	K	A	S	G	Y	T	F	T	D	Y	E	M	H	-	-	W	I	R	Q	P
GCH065	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	T	V	S	C	K	A	S	G	Y	T	F	T	D	Y	E	M	H	-	-	W	I	R	Q	P
GCH094	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	T	V	S	C	K	A	S	G	Y	T	F	T	D	Y	E	M	H	-	-	W	V	R	Q	A

Kabat CDR H2: positions 50–65; Chothia CDR H2: positions 52–56; Contact CDR H2: positions 47–58

Antibody name	41	42	43	44	45	46	47	48	49	50	51	52	52a	52b	52c	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79
CE115HA000	P	G	K	G	L	E	W	V	A	Q	I	K	A	K	S	N	N	Y	A	T	Y	Y	A	E	S	V	K	G	R	F	T	I	S	R	D	D	S	K	N	S	L	Y
TR01H040	P	G	K	G	L	E	W	V	A	Q	I	K	D	K	S	Q	N	Y	A	T	Y	Y	A	E	S	V	K	G	R	F	T	I	S	R	A	D	S	K	N	S	I	Y
TR01H071	P	G	K	G	L	E	W	V	A	Q	I	K	D	K	S	N	N	Y	A	T	Y	Y	A	E	S	V	K	G	R	F	T	I	S	R	A	D	S	K	N	S	I	Y
TR01H082	P	G	K	G	L	E	W	V	A	Q	I	K	D	K	S	Q	N	Y	A	T	Y	Y	A	E	S	V	K	G	R	F	T	I	S	R	D	D	S	K	N	S	L	Y
TR01H084	P	G	K	G	L	E	W	V	A	Q	I	K	D	K	S	Q	N	Y	A	T	Y	Y	A	E	S	V	K	G	R	F	T	I	S	R	A	D	S	K	N	S	I	Y
TR01H109	P	G	K	G	L	E	W	V	A	Q	I	K	D	K	S	Q	N	Y	A	T	Y	V	A	E	S	V	K	G	R	F	T	I	S	R	D	D	S	K	N	S	L	Y
TR01H113	P	G	K	G	L	E	W	V	A	Q	I	K	D	K	S	Q	N	Y	A	T	Y	V	A	E	S	V	K	G	R	F	T	I	S	R	A	D	S	K	N	S	I	Y
H0000	P	G	Q	G	L	E	W	I	G	A	I	D	P	-	-	K	T	G	D	T	A	Y	S	Q	K	F	K	G	R	V	T	L	T	A	D	K	S	T	S	T	A	Y
H0610	P	G	Q	G	L	E	W	I	G	A	I	D	G	-	-	K	T	P	D	T	A	Y	S	Q	K	F	K	G	R	V	T	L	T	A	D	K	S	T	S	T	A	Y
GCH054	P	G	E	G	L	E	W	I	G	A	I	D	G	-	-	E	T	P	D	T	A	Y	S	E	K	F	K	G	R	V	T	L	T	A	D	K	S	T	S	T	A	Y
GCH065	P	G	E	G	L	E	W	I	G	A	I	D	G	-	-	P	T	P	D	T	A	Y	S	E	K	F	K	G	R	V	T	L	T	A	D	K	S	T	S	T	A	Y
GCH094	P	G	E	G	L	E	W	M	G	A	I	D	G	-	-	E	T	P	D	T	A	Y	S	E	K	F	K	G	R	V	T	L	T	A	D	K	S	T	S	T	A	Y

FIG. 24-1

Antibody name	80	81	82	82a	82b	82c	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	100a	100b	100c	100d	100e	100f	100g	100h	100i	100j	100k	101	102	103	104	105	106	107
																			Kabat CDR H3																							
																	Chothia CDR H3																									
																	Contact CDR H3																									
CE115HA000	L	Q	M	N	S	L	K	T	E	D	T	A	V	Y	Y	C	R	Y	V	H	Y	G	A	Y	Y	G	V	-	-	-	-	-	-	-	-	D	A	W	G	Q	G	T
TR01H040	L	Q	M	N	S	L	K	T	E	D	T	A	V	Y	Y	C	R	Y	V	H	Y	S	A	S	Y	G	V	-	-	-	-	-	-	-	-	D	A	W	G	Q	G	T
TR01H071	L	Q	M	N	S	L	K	T	E	D	T	A	V	Y	Y	C	R	Y	V	H	Y	A	A	S	Y	G	V	-	-	-	-	-	-	-	-	D	I	W	G	Q	G	T
TR01H082	L	Q	M	N	S	L	K	T	E	D	T	A	V	Y	Y	C	R	Y	V	H	Y	A	A	G	Y	G	V	-	-	-	-	-	-	-	-	D	A	W	G	Q	G	T
TR01H084	L	Q	M	N	S	L	K	T	E	D	T	A	V	Y	Y	C	R	Y	V	H	Y	A	A	G	Y	G	V	-	-	-	-	-	-	-	-	D	I	W	G	Q	G	T
TR01H109	L	Q	M	N	S	L	K	T	E	D	T	A	V	Y	Y	C	R	Y	V	H	Y	A	A	G	Y	G	V	-	-	-	-	-	-	-	-	D	A	W	G	Q	G	T
TR01H113	L	Q	M	N	S	L	K	T	E	D	T	A	V	Y	Y	C	R	Y	V	H	Y	A	A	G	Y	G	V	-	-	-	-	-	-	-	-	D	I	W	G	Q	G	T
H0000	M	E	L	S	S	L	T	S	E	D	T	A	V	Y	Y	C	T	R	F	Y	S	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	T	Y	W	G	Q	G	T
H0610	M	E	L	S	S	L	T	S	E	D	T	A	V	Y	Y	C	T	R	F	Y	S	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	T	Y	W	G	Q	G	T
GCH054	M	E	L	S	S	L	T	S	E	D	T	A	V	Y	Y	C	T	R	F	Y	S	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	T	Y	W	G	Q	G	T
GCH065	M	E	L	S	S	L	T	S	E	D	T	A	V	Y	Y	C	T	R	F	Y	S	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	T	Y	W	G	Q	G	T
GCH094	M	E	L	S	S	L	T	S	E	D	T	A	V	Y	Y	C	T	R	F	Y	S	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	T	Y	W	G	Q	G	T

Antibody name	108	109	110	111	112	113
CE115HA000	T	V	T	V	S	S
TR01H040	T	V	T	V	S	S
TR01H071	T	V	T	V	S	S
TR01H082	T	V	T	V	S	S
TR01H084	T	V	T	V	S	S
TR01H109	T	V	T	V	S	S
TR01H113	T	V	T	V	S	S
H0000	L	V	T	V	S	S
H0610	L	V	T	V	S	S
GCH054	L	V	T	V	S	S
GCH065	L	V	T	V	S	S
GCH094	L	V	T	V	S	S

FIG. 24-2

Antibody name	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	27a	27b	27c	27d	27e	27f	28	29	30	31	32	33	34	35	36
																								Kabat CDR L1																		
																								Chothia CDR L1																		
																																				Contact CDR L1						
L0000	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	Q	S	L	V	H	S	-	N	R	N	T	Y	L	H	W	Y
L0011	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	Q	P	L	V	H	S	-	N	R	N	T	Y	L	H	W	Y
L0201	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	Q	P	P	V	H	S	-	N	R	N	T	Y	L	H	W	Y
L0203	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	Q	S	P	V	H	S	-	N	R	N	T	Y	I	H	W	Y
L0204	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	Q	S	P	V	H	S	-	N	R	N	T	Y	L	H	W	Y
L0206	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	Q	S	P	V	H	S	-	N	R	N	T	Y	L	H	W	Y
L0208	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	Q	S	P	V	H	S	-	N	R	N	T	Y	L	H	W	Y
L0209	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	Q	S	P	V	H	S	-	N	R	N	T	Y	I	H	W	Y
L0211	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	Q	P	P	V	H	S	-	N	R	N	T	Y	L	H	W	Y
L0212	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	P	S	Q	S	P	V	H	S	-	N	R	N	T	Y	L	H	W	Y
L0222	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	Q	S	P	V	H	S	-	N	R	N	T	Y	I	Q	W	Y
L0272	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	Q	P	L	V	H	S	-	N	R	Q	T	Y	L	H	W	Y

Antibody name	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78
														Kabat CDR L2																												
														Chothia CDR L2																												
										Contact CDR L2																																
L0000	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0011	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0201	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0203	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0204	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	R	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0206	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0208	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	W	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0209	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0211	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0212	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0222	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0272	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V

Antibody name	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	95a	95b	95c	95d	95e	95f	96	97	98	99	100	101	102	103	104	105	106	107
											Kabat CDR L3																								
											Chothia CDR L3																								
											Contact CDR L3																								
L0000	E	A	E	D	V	G	V	Y	Y	C	G	Q	G	T	Q	V	P	-	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K
L0011	E	A	E	D	V	G	V	Y	Y	C	G	Q	G	T	Q	V	P	-	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K
L0201	E	A	E	D	V	G	V	Y	Y	C	G	Q	G	T	Q	V	P	-	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K
L0203	E	A	E	D	V	G	V	Y	Y	C	G	Q	G	T	Q	V	P	-	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K
L0204	E	A	E	D	V	G	V	Y	Y	C	G	Q	G	T	Q	V	P	-	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K
L0206	E	A	E	D	V	G	V	Y	Y	C	Y	Q	G	T	Q	V	P	-	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K
L0208	E	A	E	D	V	G	V	Y	Y	C	Y	Q	G	T	Q	V	P	-	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K
L0209	E	A	E	D	V	G	V	Y	Y	C	Y	Q	G	T	Q	V	P	-	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K
L0211	E	A	E	D	V	G	V	Y	Y	C	Y	Q	G	T	Q	V	P	-	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K
L0212	E	A	E	D	V	G	V	Y	Y	C	Y	Q	G	T	Q	V	P	-	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K
L0222	E	A	E	D	V	G	V	Y	Y	C	Y	Q	G	T	Q	V	P	-	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K
L0272	E	A	E	D	V	G	V	Y	Y	C	G	Q	G	T	Q	V	P	-	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K

FIG. 25

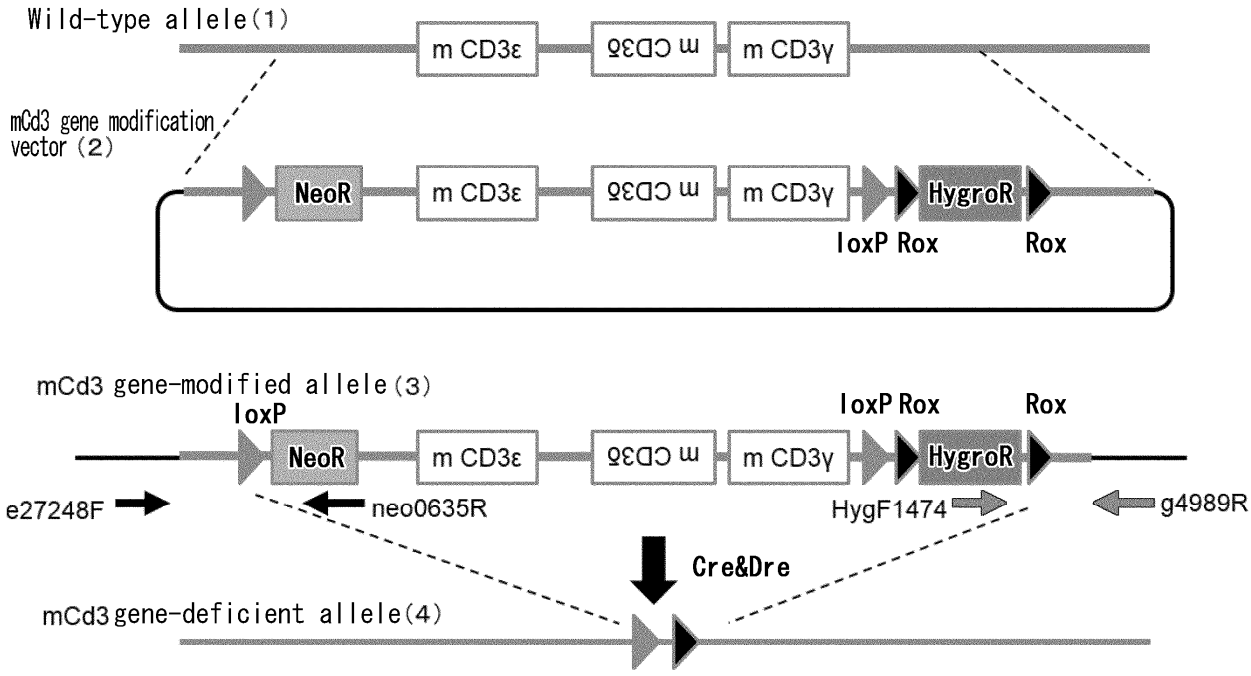

Wild-type allele(1)
m CD3ε
m CD3δ
m CD3γ
mCd3 gene modification vector (2)
NeoR
HygroR
loxP Rox
Rox
mCd3 gene-modified allele(3)
loxP
e27248F
neo0635R
HygF1474
g4989R
Cre&Dre
mCd3 gene-deficient allele(4)

FIG. 26A

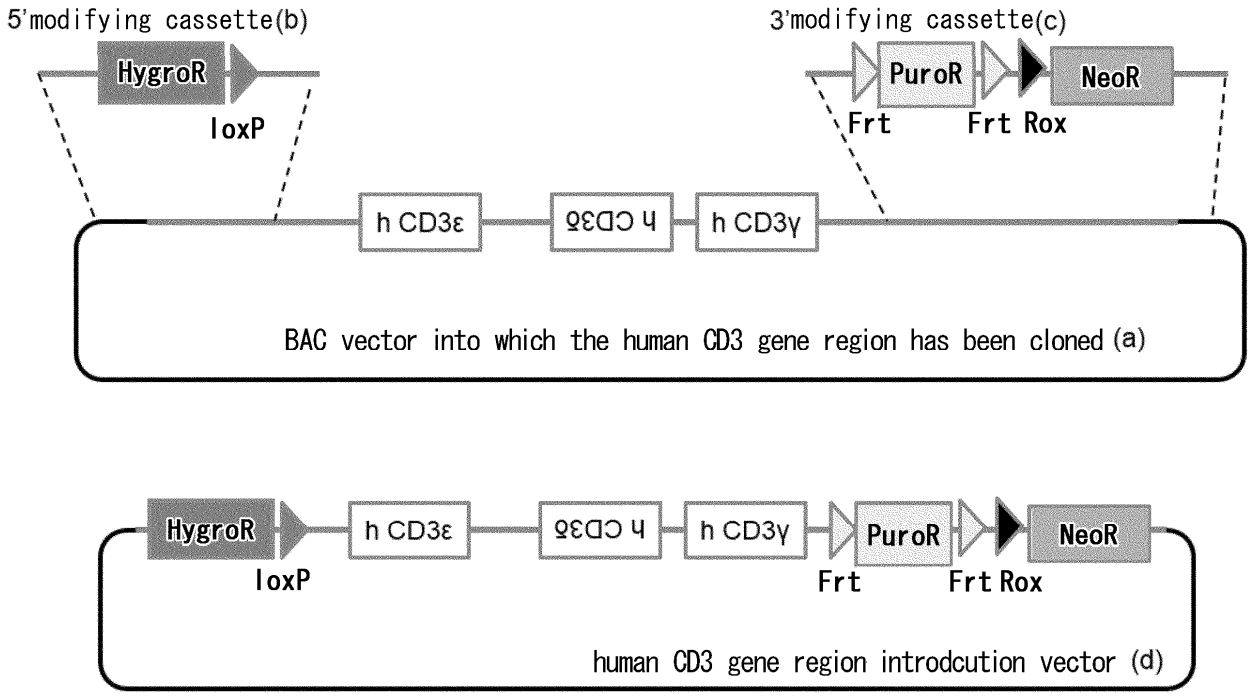

5'modifying cassette(b)
HygroR
loxP
3'modifying cassette(c)
PuroR
NeoR
Frt
Frt Rox
h CD3ε
h CD3γ
BAC vector into which the human CD3 gene region has been cloned (a)
HygroR
loxP
h CD3ε
h CD3γ
PuroR
NeoR
Frt
Frt Rox
human CD3 gene region introdcution vector (d)

FIG. 26B

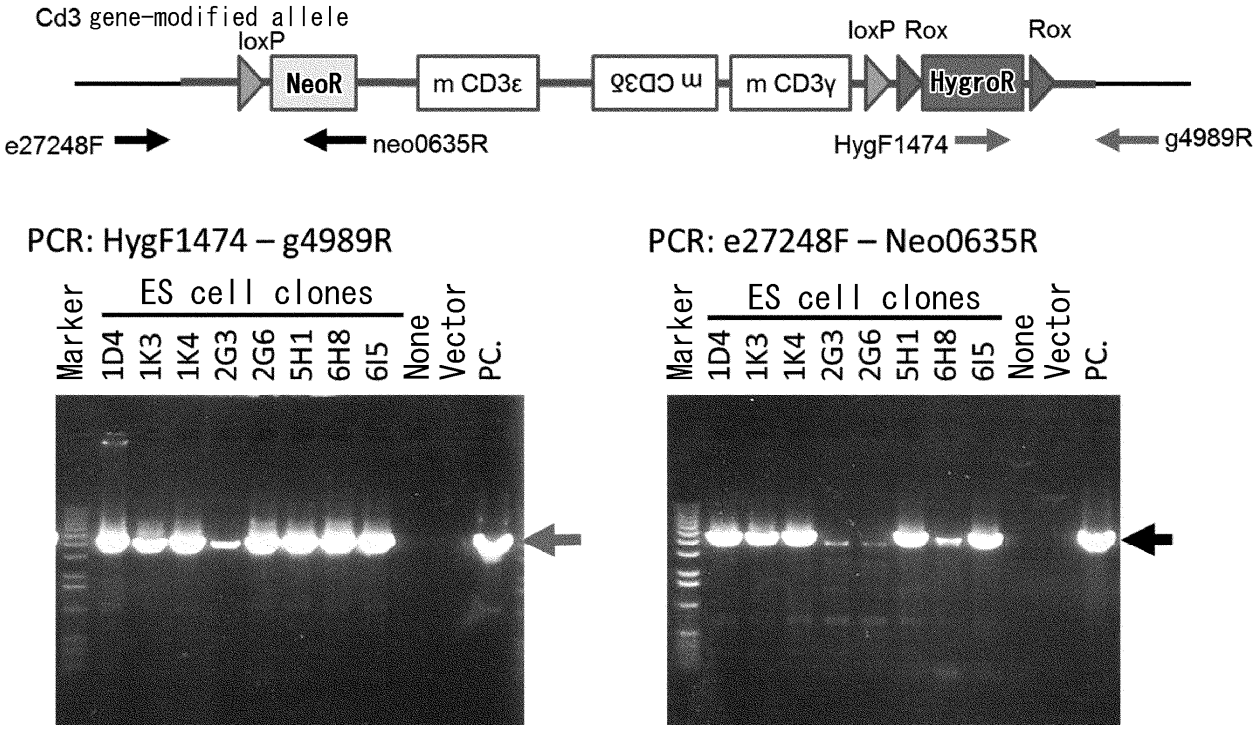

Cd3 gene-modified allele
loxP
NeoR
m CD3ε
m CD3δ
m CD3γ
loxP Rox
Rox
HygroR
e27248F
neo0635R
HygF1474
g4989R
PCR: HygF1474 – g4989R
Marker
ES cell clones
1D4
1K3
1K4
2G3
2G6
5H1
6H8
6I5
None
Vector
PC.
PCR: e27248F – Neo0635R
Marker
ES cell clones
1D4
1K3
1K4
2G3
2G6
5H1
6H8
6I5
None
Vector
PC.

FIG. 27

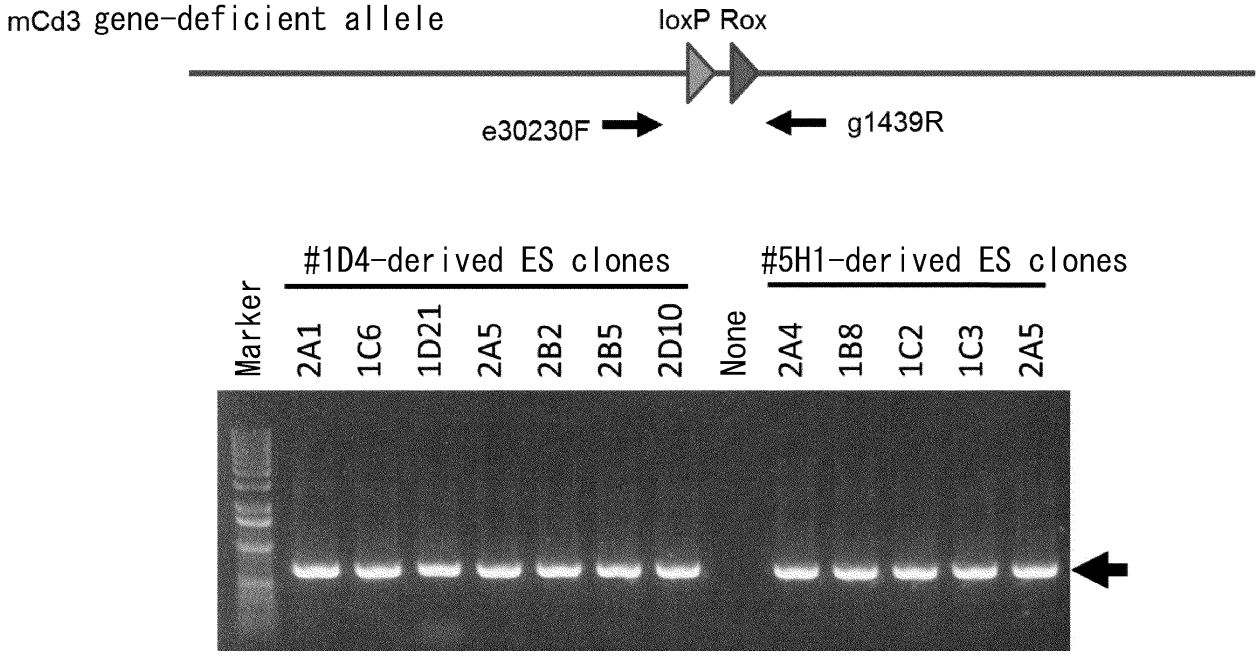

mCd3 gene-deficient allele
loxP Rox
e30230F
g1439R
#1D4-derived ES clones
#5H1-derived ES clones
Marker
2A1
1C6
1D21
2A5
2B2
2B5
2D10
None
2A4
1B8
1C2
1C3
2A5

FIG. 28A

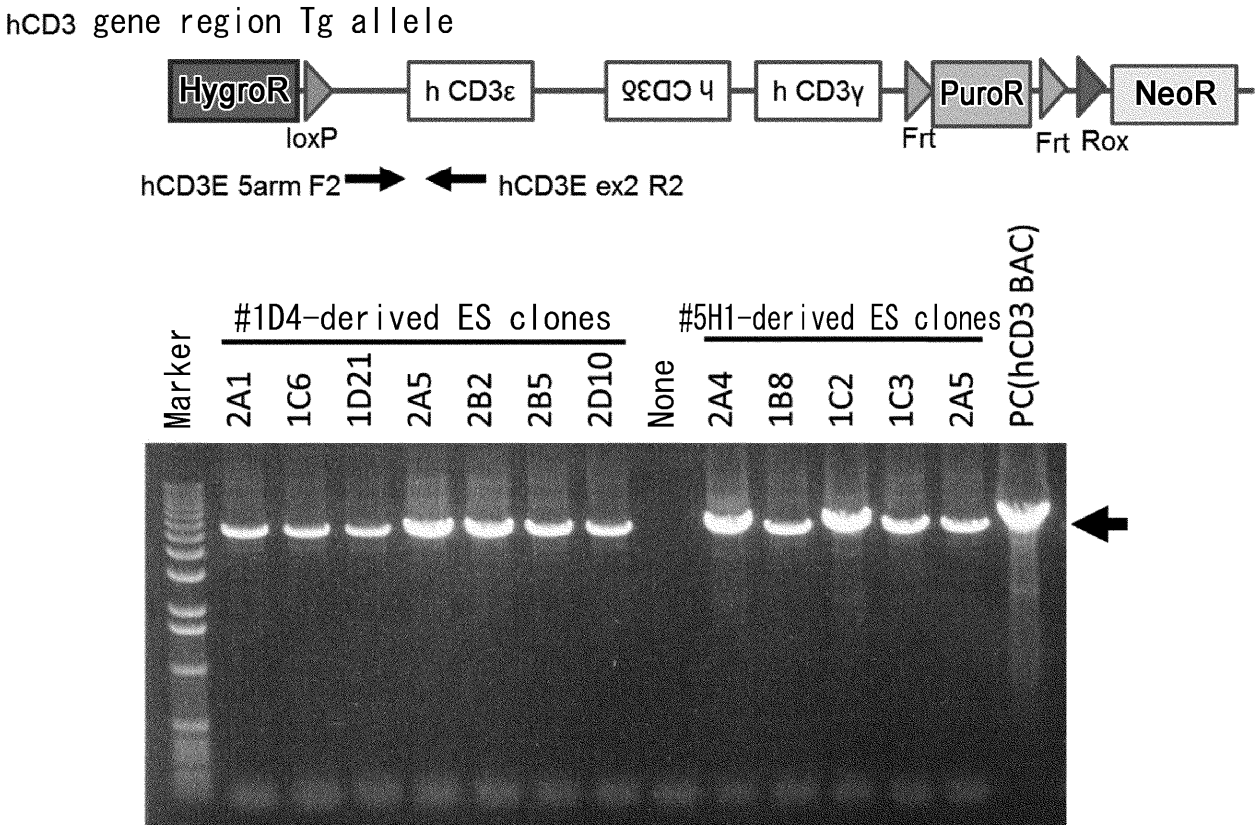

hCD3 gene region Tg allele
HygroR
loxP
h CD3ε
h CD3γ
PuroR
Frt
Frt Rox
NeoR
hCD3E 5arm F2
hCD3E ex2 R2
#1D4-derived ES clones
#5H1-derived ES clones
Marker
2A1
1C6
1D21
2A5
2B2
2B5
2D10
None
2A4
1B8
1C2
1C3
2A5
PC(hCD3 BAC)

FIG. 28B

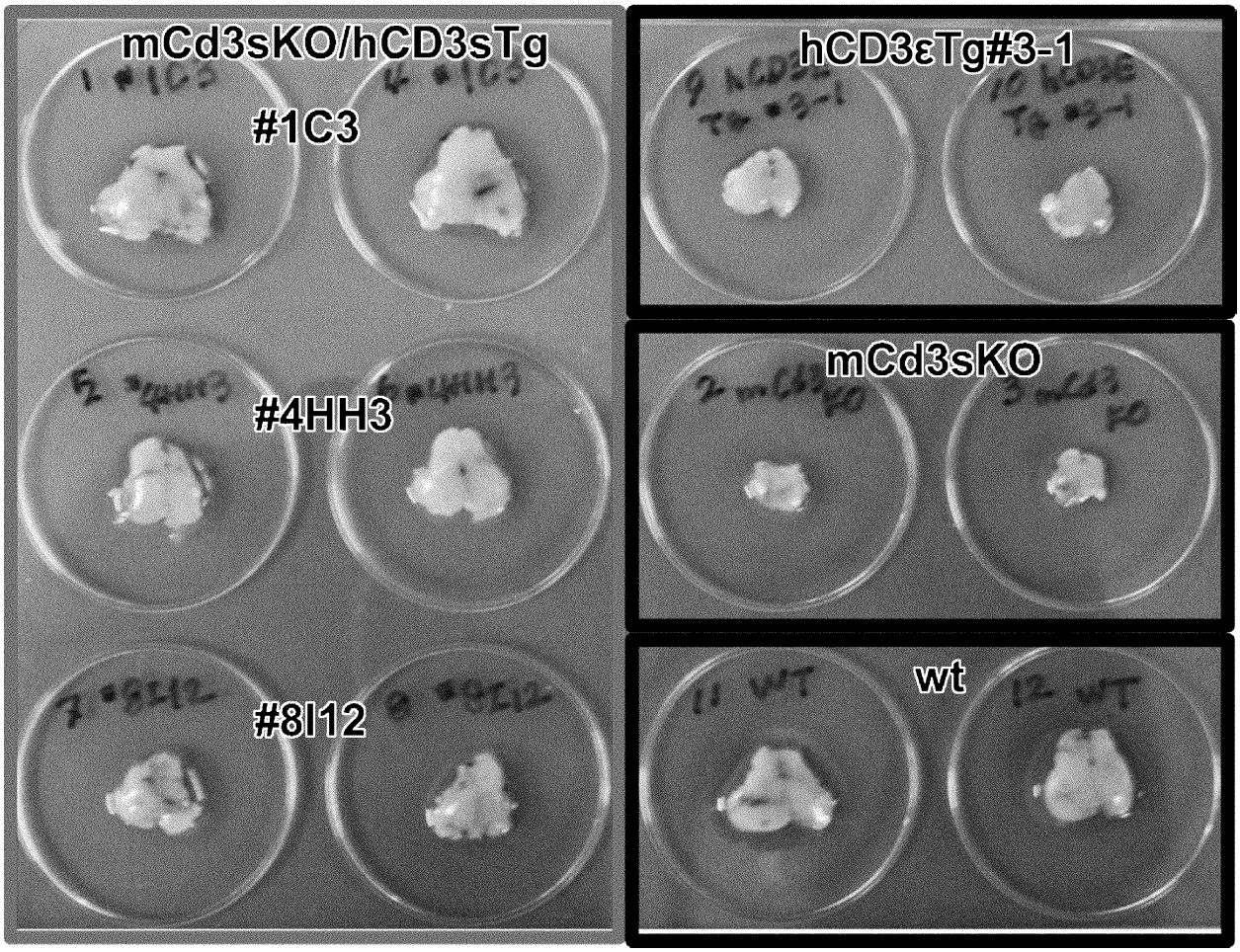


FIG. 29

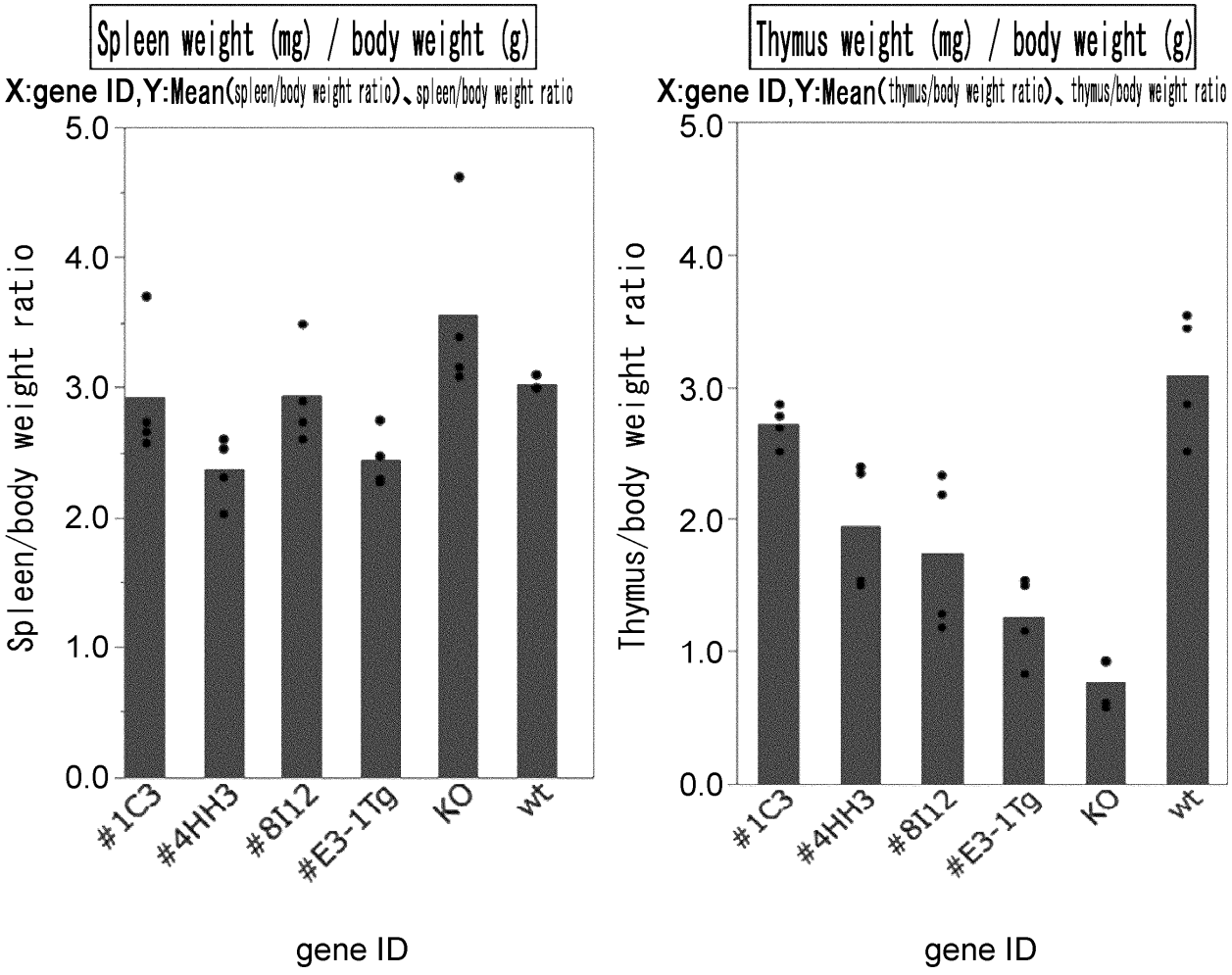

Spleen weight (mg) / body weight (g)
X:gene ID,Y:Mean(spleen/body weight ratio)、spleen/body weight ratio
Spleen/body weight ratio
5.0
4.0
3.0
2.0
1.0
0.0
#1C3
#4HH3
#8I12
#E3-1Tg
KO
wt
gene ID
Thymus weight (mg) / body weight (g)
X:gene ID,Y:Mean(thymus/body weight ratio)、thymus/body weight ratio
Thymus/body weight ratio
5.0
4.0
3.0
2.0
1.0
0.0
#1C3
#4HH3
#8I12
#E3-1Tg
KO
wt
gene ID

FIG. 30

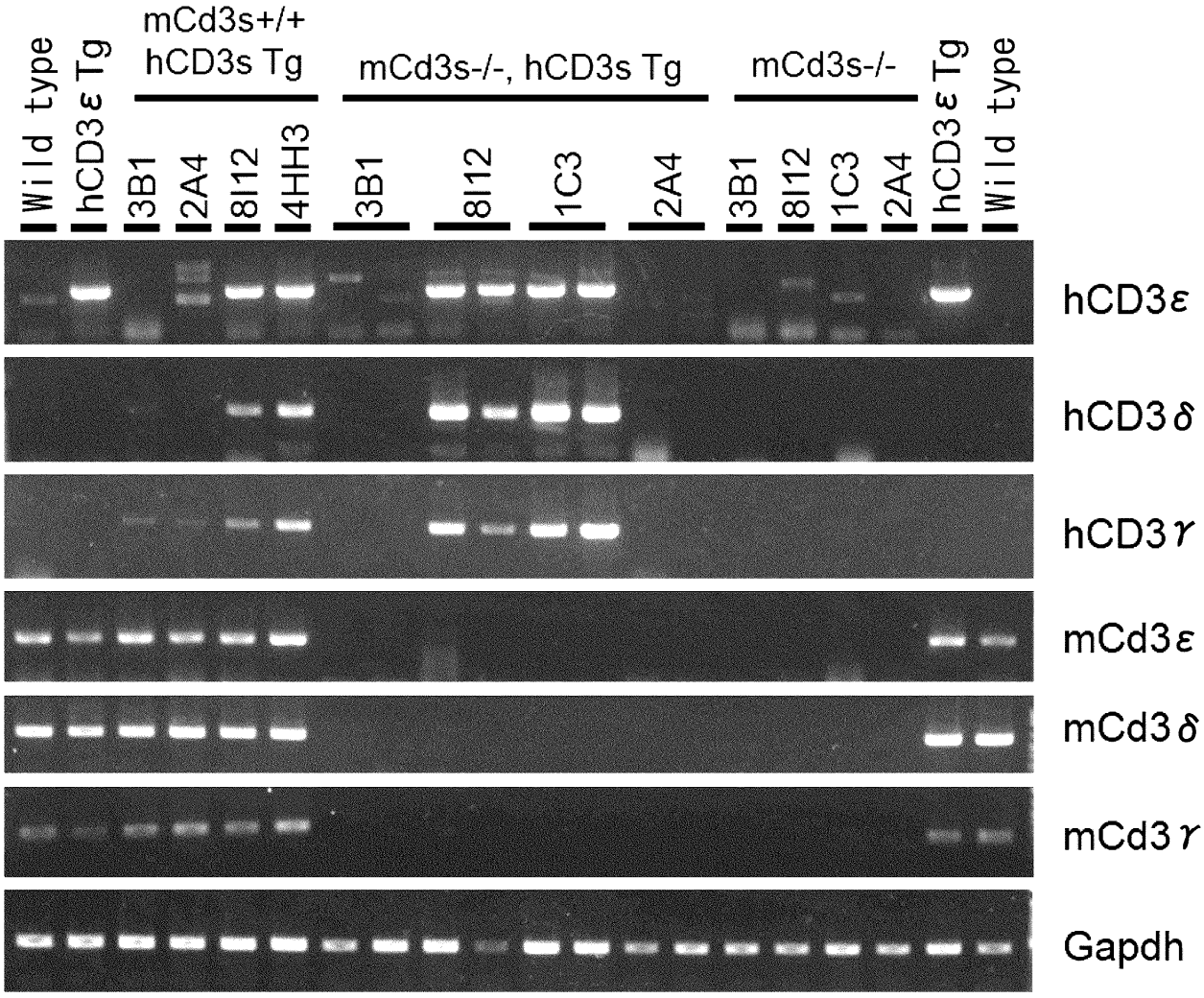

Wild type
hCD3ε Tg
mCd3s+/+ hCD3s Tg
3B1
2A4
8I12
4HH3
mCd3s-/-, hCD3s Tg
3B1
8I12
1C3
2A4
mCd3s-/-
3B1
8I12
1C3
2A4
hCD3ε Tg
Wild type
hCD3ε
hCD3δ
hCD3γ
mCd3ε
mCd3δ
mCd3γ
Gapdh

FIG. 31

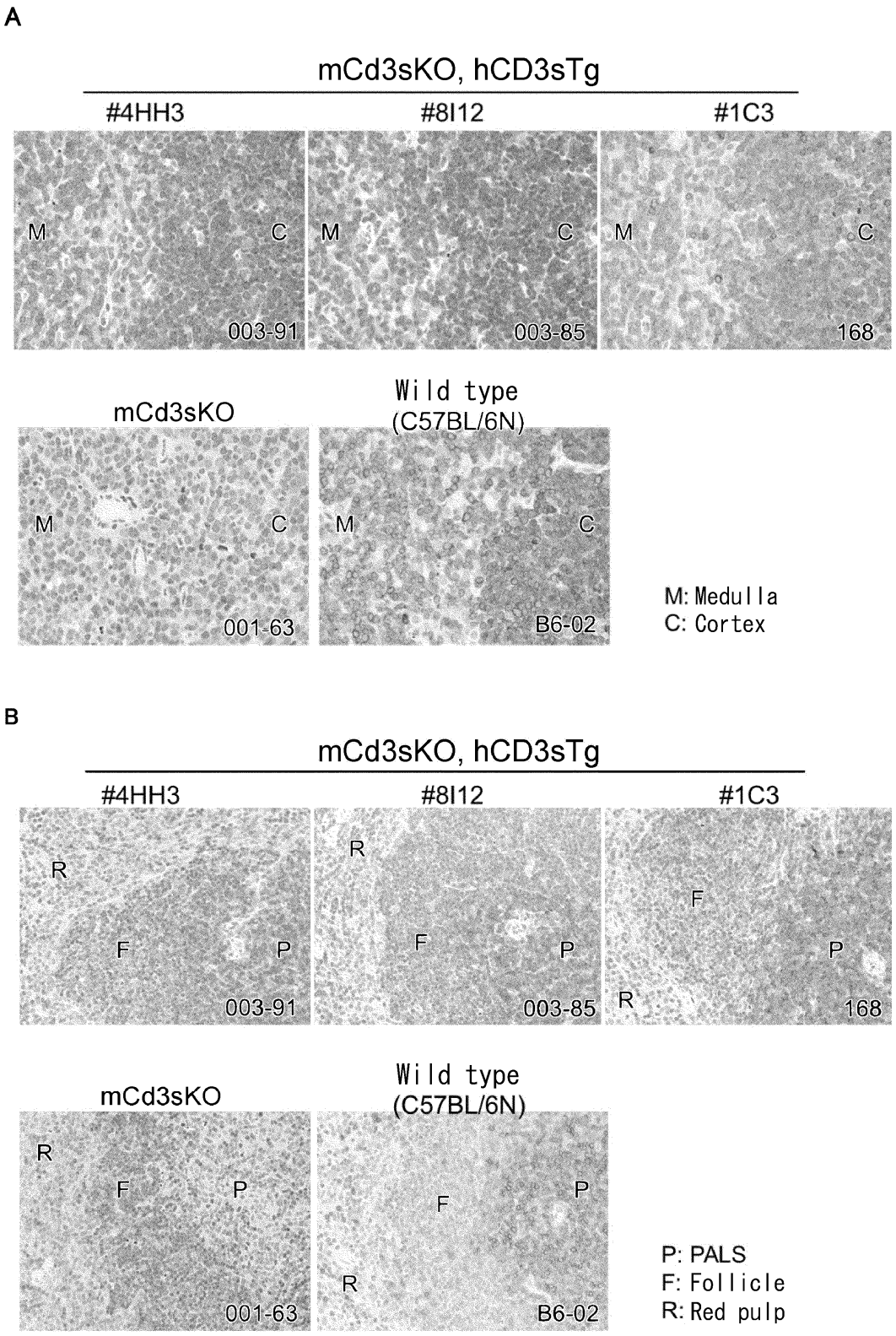

A
mCd3sKO, hCD3sTg
#4HH3
#8I12
#1C3
M
C
003-91
003-85
168
mCd3sKO
Wild type
(C57BL/6N)
001-63
B6-02
M: Medulla
C: Cortex
B
mCd3sKO, hCD3sTg
#4HH3
#8I12
#1C3
R
F
P
003-91
003-85
168
mCd3sKO
Wild type
(C57BL/6N)
001-63
B6-02
P: PALS
F: Follicle
R: Red pulp

FIG. 32

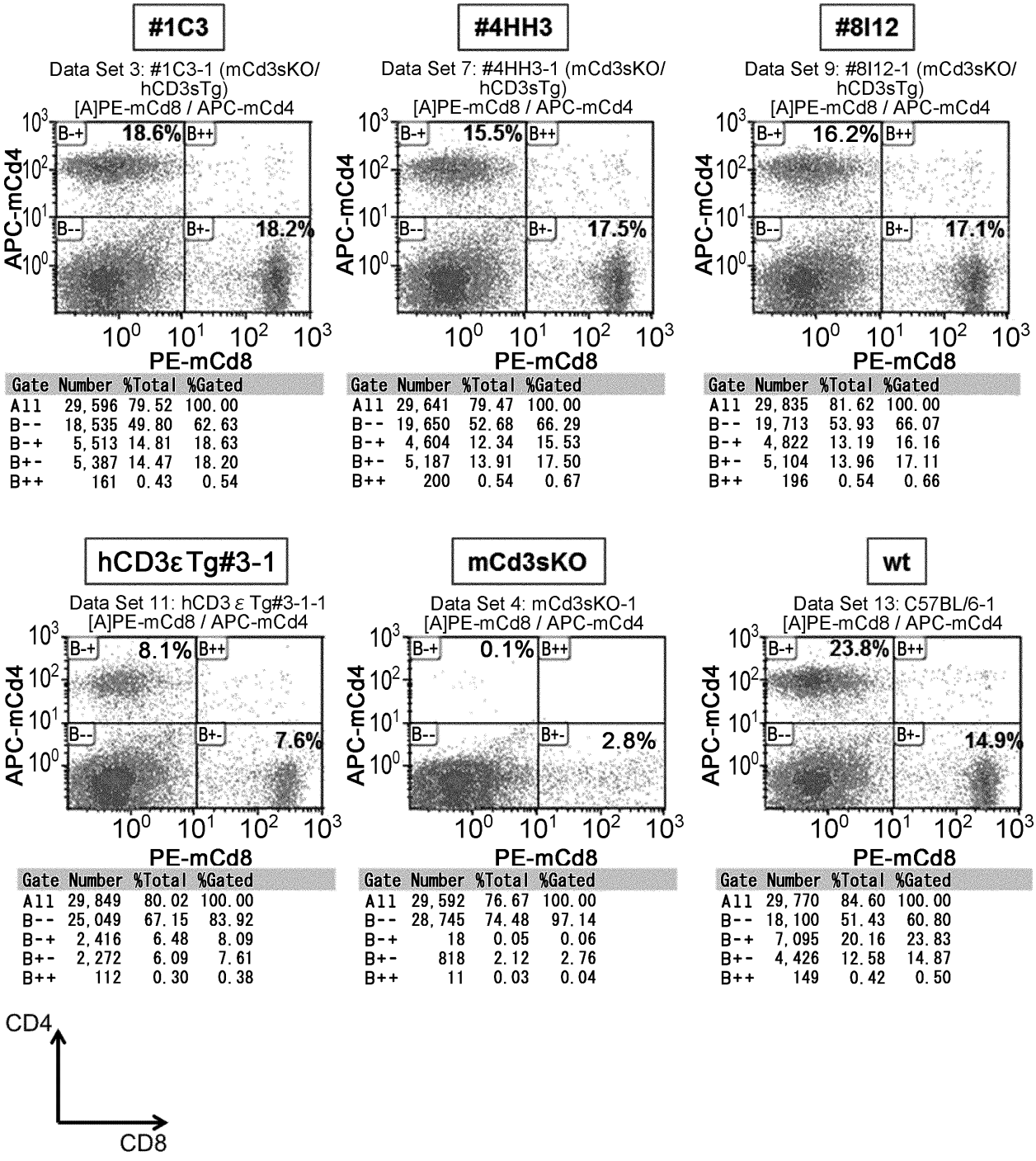

#1C3
Data Set 3: #1C3-1 (mCd3sKO/ hCD3sTg)
[A]PE-mCd8 / APC-mCd4
B-+ 18.6%
B++
B-- B+- 18.2%
APC-mCd4
PE-mCd8
Gate Number %Total %Gated
All 29,596 79.52 100.00
B-- 18,535 49.80 62.63
B-+ 5,513 14.81 18.63
B+- 5,387 14.47 18.20
B++ 161 0.43 0.54
#4HH3
Data Set 7: #4HH3-1 (mCd3sKO/ hCD3sTg)
[A]PE-mCd8 / APC-mCd4
B-+ 15.5%
B++
B-- B+- 17.5%
APC-mCd4
PE-mCd8
Gate Number %Total %Gated
All 29,641 79.47 100.00
B-- 19,650 52.68 66.29
B-+ 4,604 12.34 15.53
B+- 5,187 13.91 17.50
B++ 200 0.54 0.67
#8I12
Data Set 9: #8I12-1 (mCd3sKO/ hCD3sTg)
[A]PE-mCd8 / APC-mCd4
B-+ 16.2%
B++
B-- B+- 17.1%
APC-mCd4
PE-mCd8
Gate Number %Total %Gated
All 29,835 81.62 100.00
B-- 19,713 53.93 66.07
B-+ 4,822 13.19 16.16
B+- 5,104 13.96 17.11
B++ 196 0.54 0.66
hCD3εTg#3-1
Data Set 11: hCD3 ε Tg#3-1-1
[A]PE-mCd8 / APC-mCd4
B-+ 8.1%
B++
B-- B+- 7.6%
APC-mCd4
PE-mCd8
Gate Number %Total %Gated
All 29,849 80.02 100.00
B-- 25,049 67.15 83.92
B-+ 2,416 6.48 8.09
B+- 2,272 6.09 7.61
B++ 112 0.30 0.38
mCd3sKO
Data Set 4: mCd3sKO-1
[A]PE-mCd8 / APC-mCd4
B-+ 0.1%
B++
B-- B+- 2.8%
APC-mCd4
PE-mCd8
Gate Number %Total %Gated
All 29,592 76.67 100.00
B-- 28,745 74.48 97.14
B-+ 18 0.05 0.06
B+- 818 2.12 2.76
B++ 11 0.03 0.04
wt
Data Set 13: C57BL/6-1
[A]PE-mCd8 / APC-mCd4
B-+ 23.8%
B++
B-- B+- 14.9%
APC-mCd4
PE-mCd8
Gate Number %Total %Gated
All 29,770 84.60 100.00
B-- 18,100 51.43 60.80
B-+ 7,095 20.16 23.83
B+- 4,426 12.58 14.87
B++ 149 0.42 0.50
CD4
CD8

FIG. 33

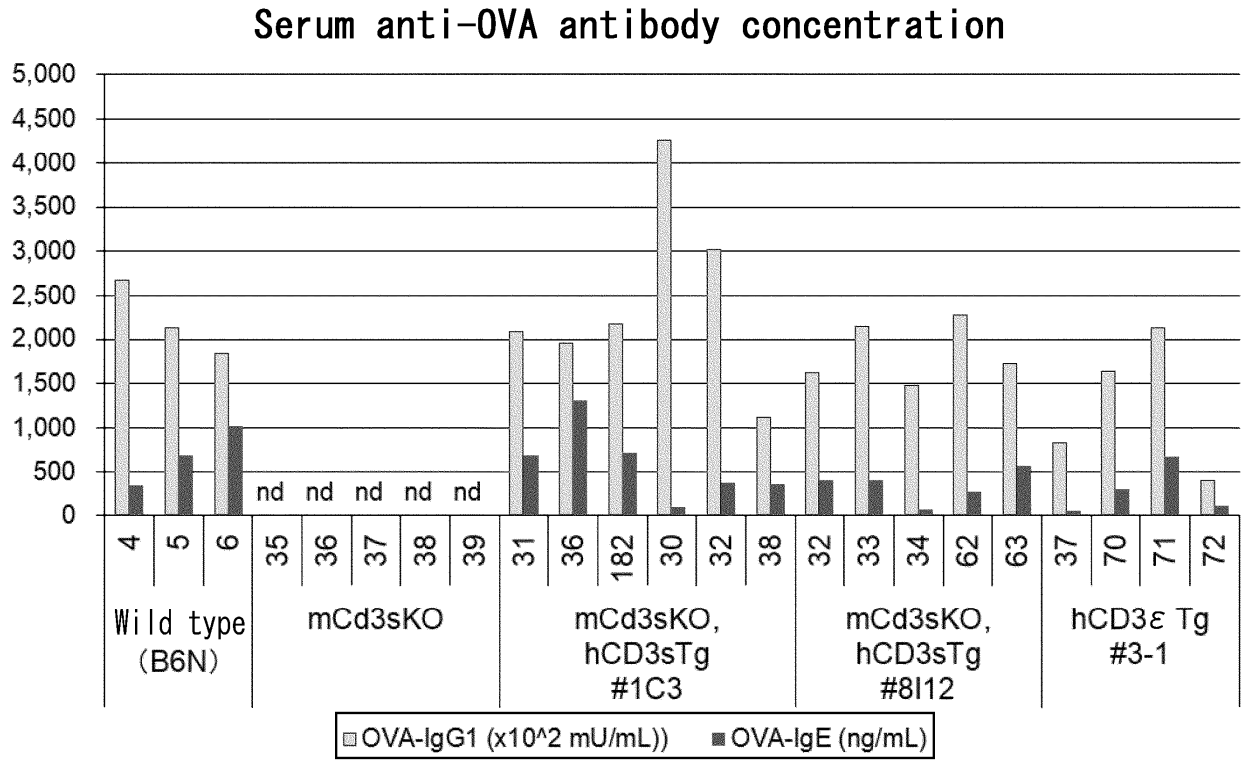

Serum anti-OVA antibody concentration
5,000
4,500
4,000
3,500
3,000
2,500
2,000
1,500
1,000
500
0
nd nd nd nd nd
4 5 6 35 36 37 38 39 31 36 182 30 32 38 32 33 34 62 63 37 70 71 72
Wild type (B6N)
mCd3sKO
mCd3sKO, hCD3sTg #1C3
mCd3sKO, hCD3sTg #8I12
hCD3ε Tg #3-1
OVA-IgG1 (x10^2 mU/mL))
OVA-IgE (ng/mL)

FIG. 34

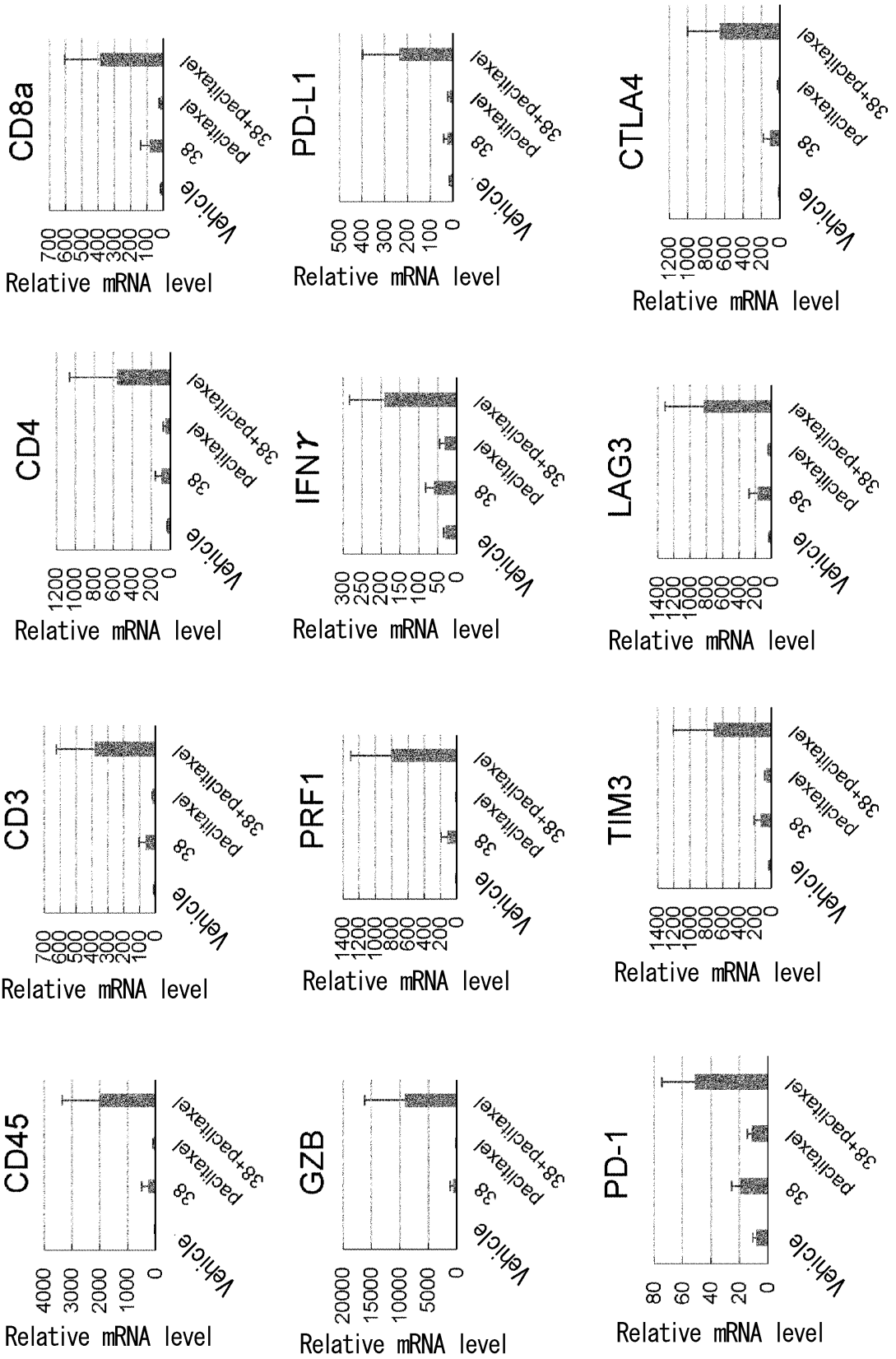

CD8a
PD-L1
CTLA4
CD4
IFNγ
LAG3
CD3
PRF1
TIM3
CD45
GZB
PD-1
Vehicle
38
Paclitaxel
38+Paclitaxel
Relative mRNA level

FIG. 35-1

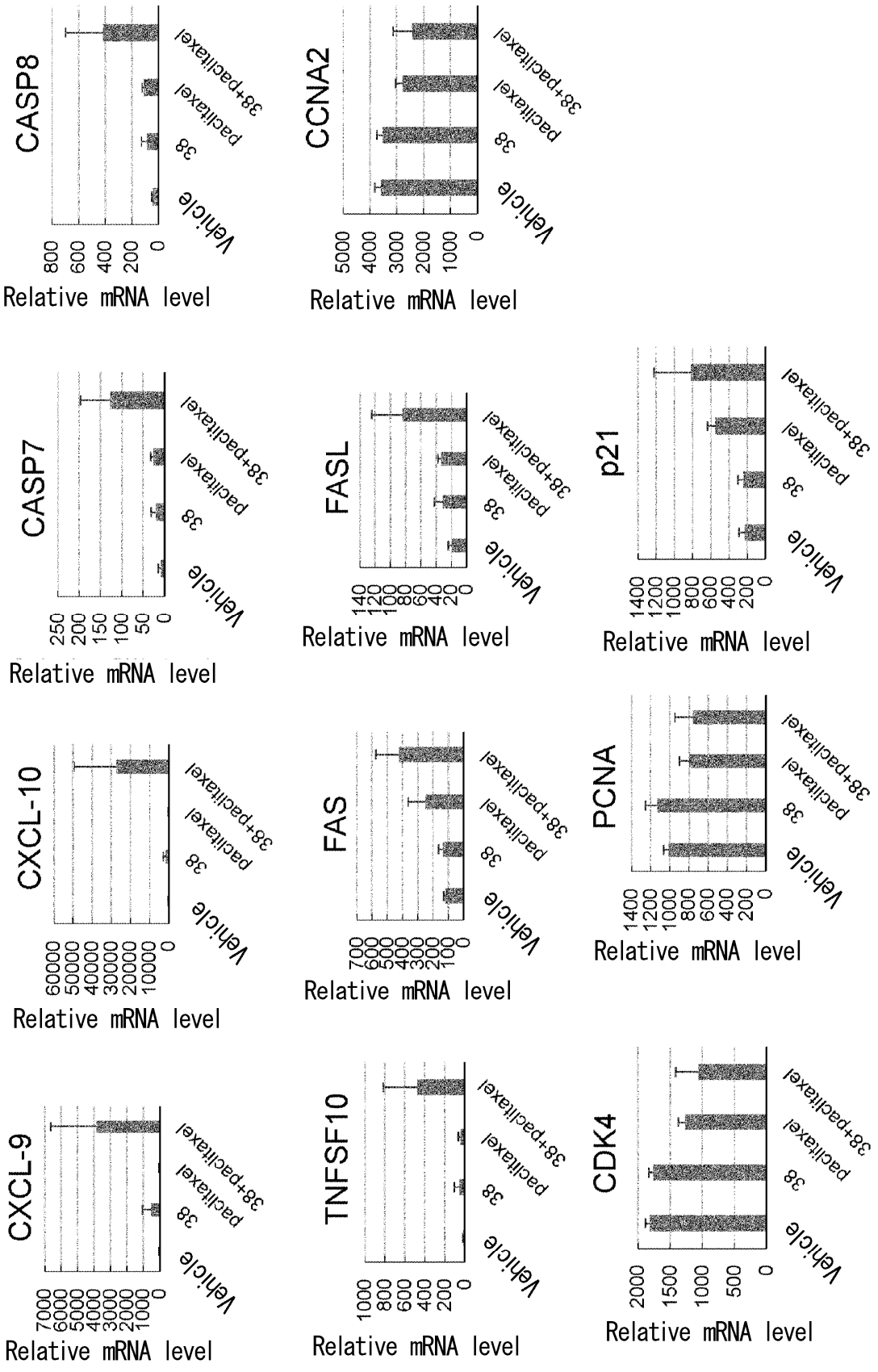

CASP8
Vehicle
38
paclitaxel
38+paclitaxel
Relative mRNA level
CCNA2
CASP7
FASL
p21
CXCL-10
FAS
PCNA
CXCL-9
TNFSF10
CDK4

FIG. 35-2

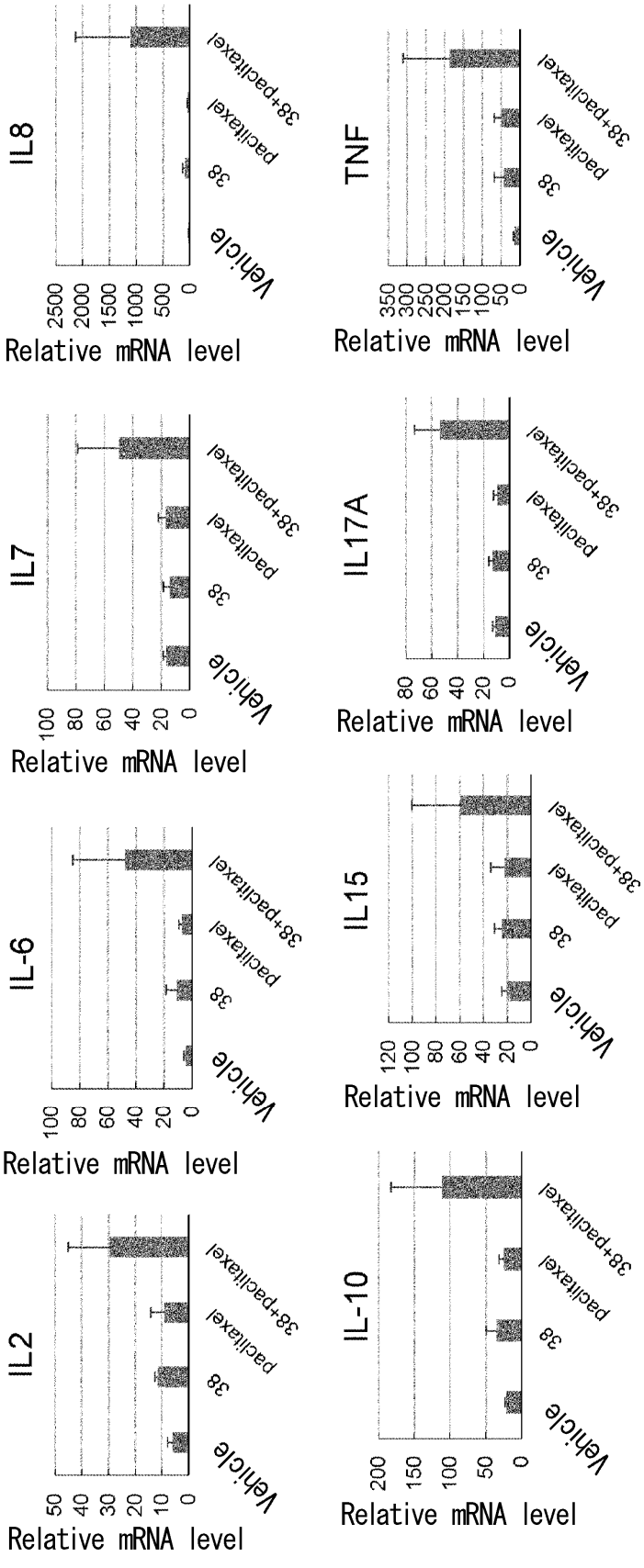

IL8
Relative mRNA level
2500
2000
1500
1000
500
0
Vehicle
38
paclitaxel
38+paclitaxel
TNF
Relative mRNA level
350
300
250
200
150
100
50
0
IL7
Relative mRNA level
100
80
60
40
20
0
IL17A
Relative mRNA level
80
60
40
20
0
IL-6
Relative mRNA level
100
80
60
40
20
0
IL15
Relative mRNA level
120
100
80
60
40
20
0
IL2
Relative mRNA level
50
40
30
20
10
0
IL-10
Relative mRNA level
200
150
100
50
0

FIG. 35-3

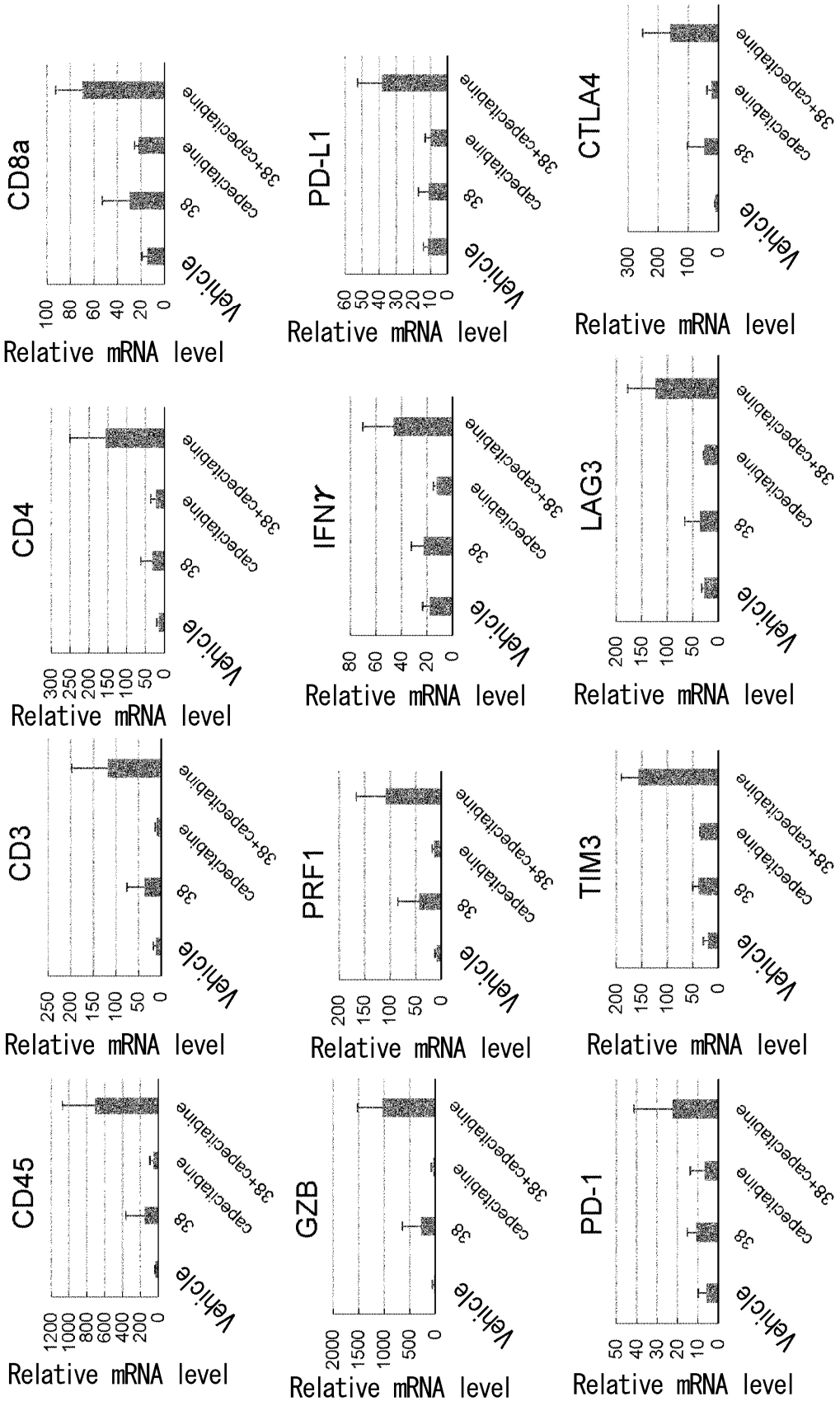

CD8a
PD-L1
CTLA4
CD4
IFNγ
LAG3
CD3
PRF1
TIM3
CD45
GZB
PD-1
Relative mRNA level
Vehicle
38
capecitabine
38+capecitabine

FIG. 35-4

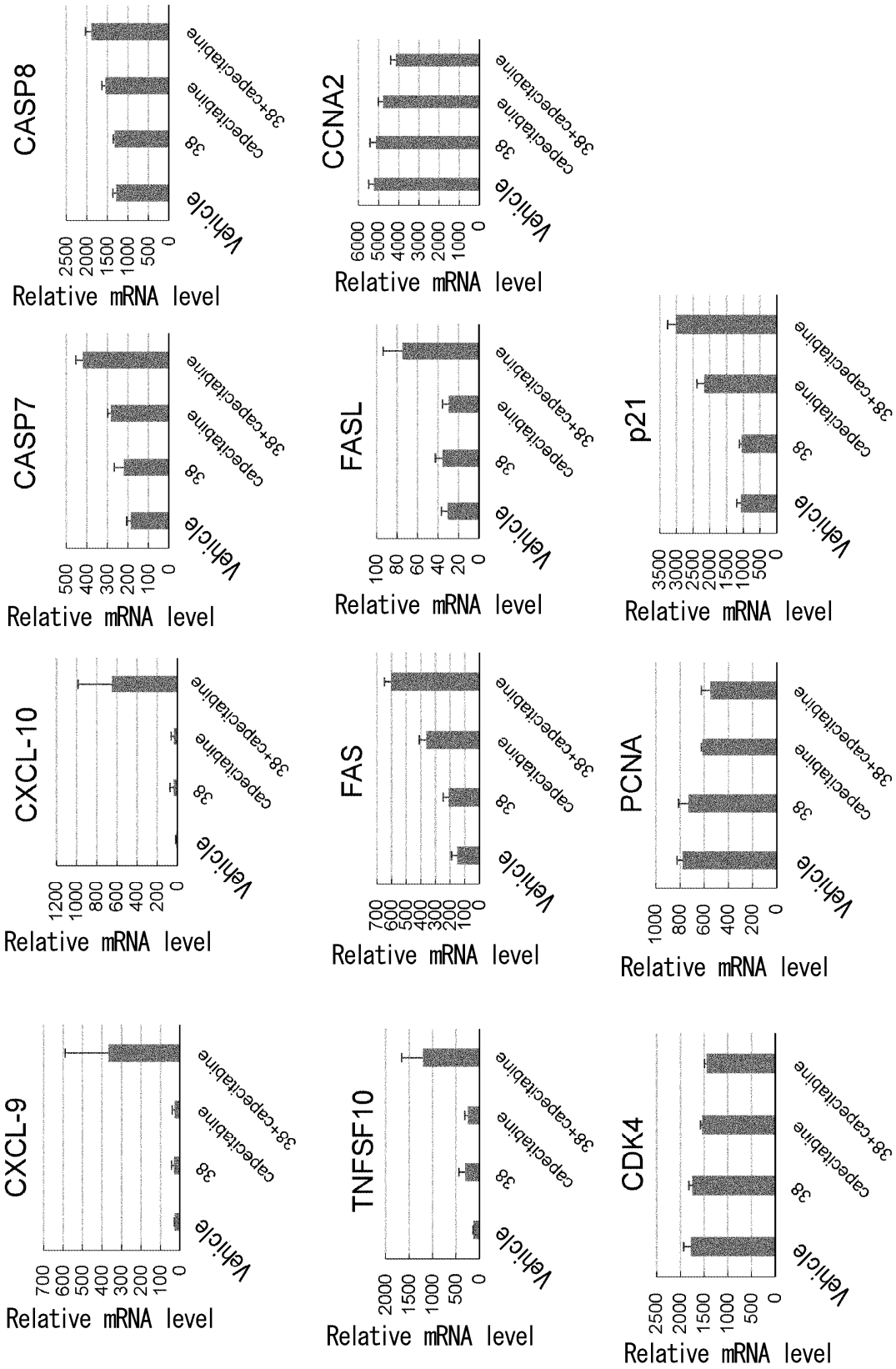

CASP8
CCNA2
CASP7
FASL
p21
CXCL-10
FAS
PCNA
CXCL-9
TNFSF10
CDK4
Relative mRNA level
Vehicle
38
capecitabine
38+capecitabine

FIG. 35-5

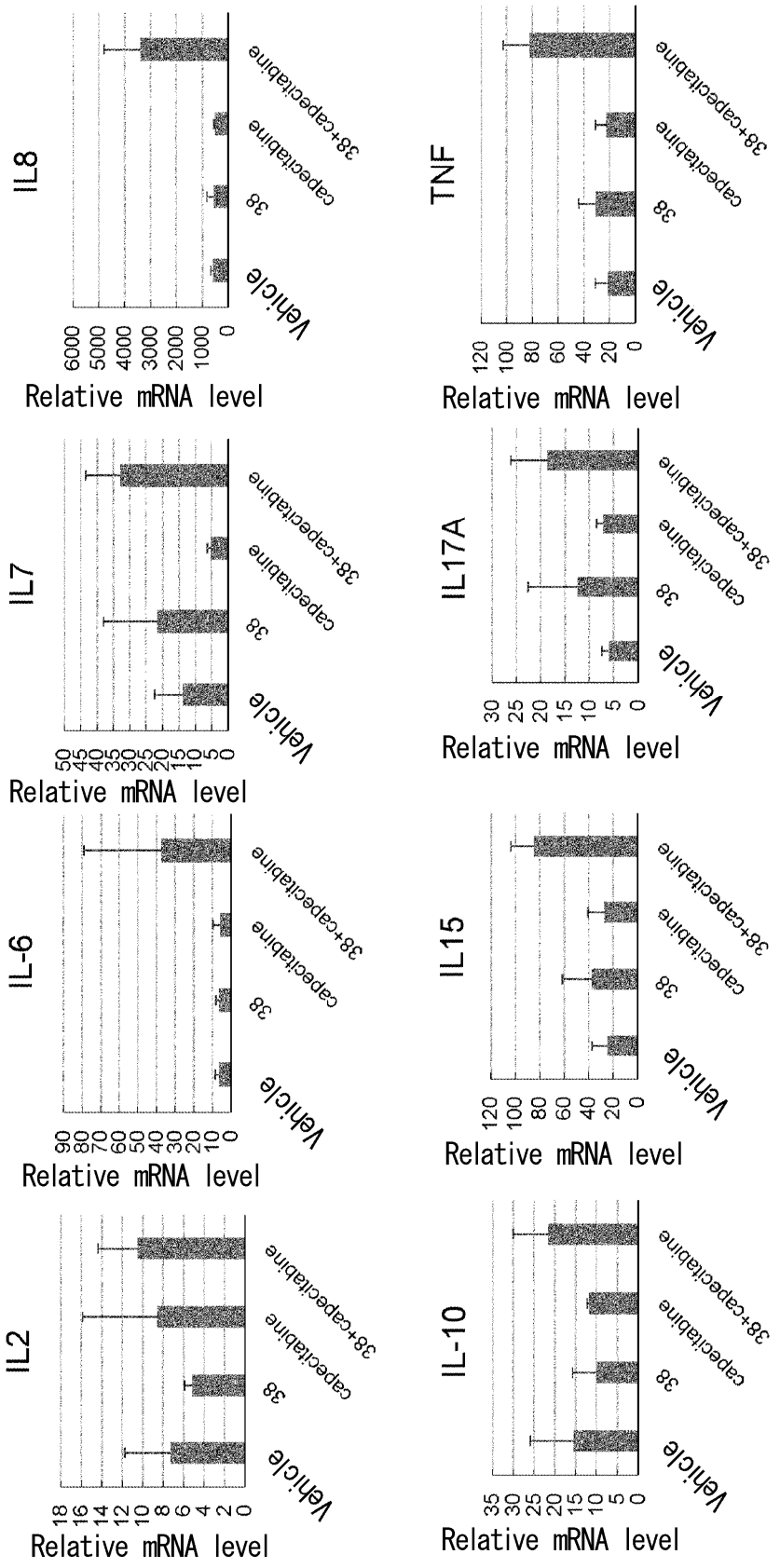

IL8
Relative mRNA level
6000
5000
4000
3000
2000
1000
0
Vehicle
38
capecitabine
38+capecitabine
TNF
Relative mRNA level
120
100
80
60
40
20
0
IL7
Relative mRNA level
50
45
40
35
30
25
20
15
10
5
0
IL17A
Relative mRNA level
30
25
20
15
10
5
0
IL-6
Relative mRNA level
90
80
70
60
50
40
30
20
10
0
IL15
Relative mRNA level
120
100
80
60
40
20
0
IL2
Relative mRNA level
18
16
14
12
10
8
6
4
2
0
IL-10
Relative mRNA level
35
30
25
20
15
10
5
0

FIG. 35-6

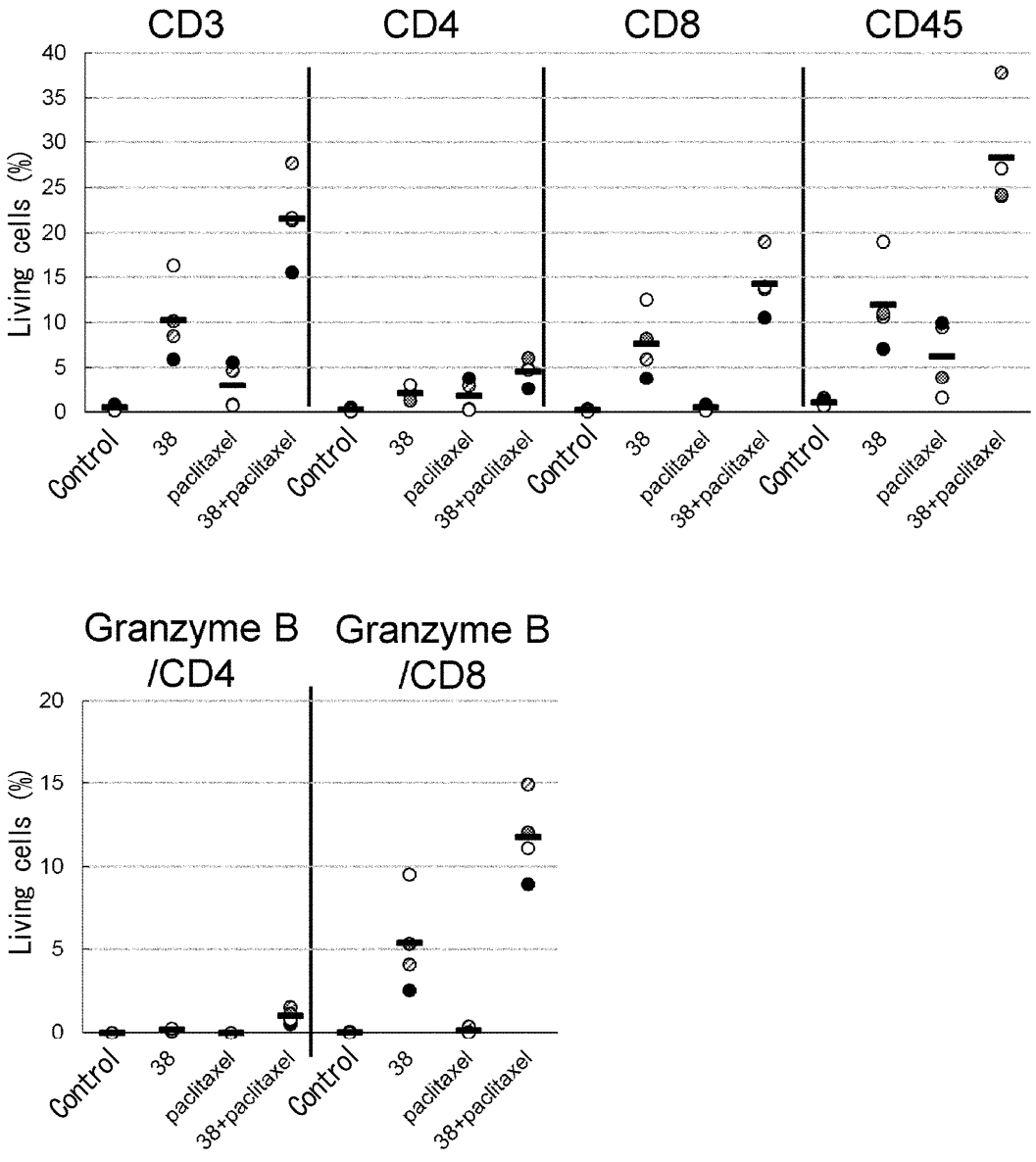

CD3
CD4
CD8
CD45
Living cells (%)
40
35
30
25
20
15
10
5
0
Control
38
paclitaxel
38+paclitaxel
Granzyme B /CD4
Granzyme B /CD8

FIG. 36-1

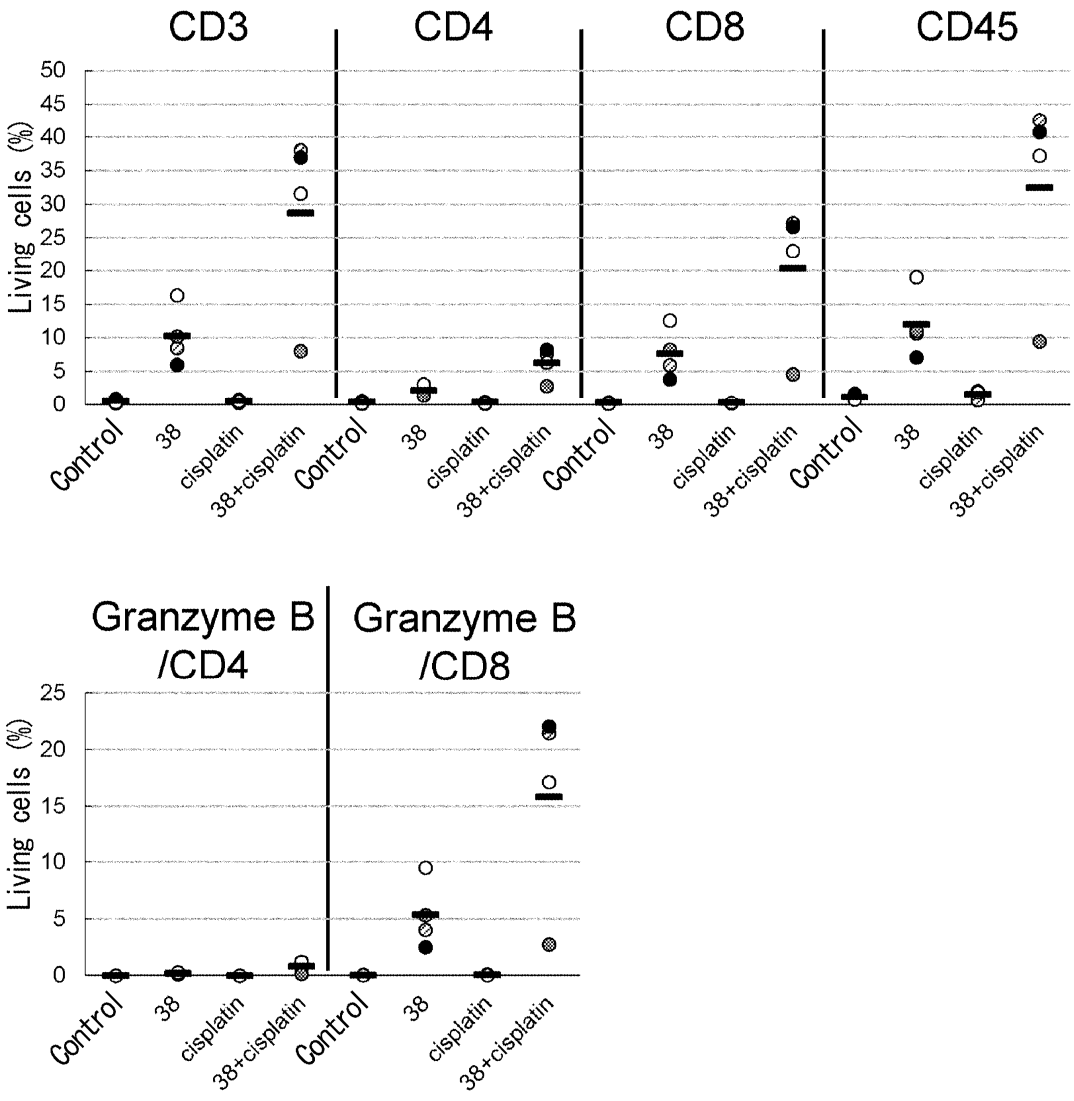

CD3
CD4
CD8
CD45
Living cells (%)
50
45
40
35
30
25
20
15
10
5
0
Control
38
cisplatin
38+cisplatin
Granzyme B /CD4
Granzyme B /CD8

FIG. 36-2