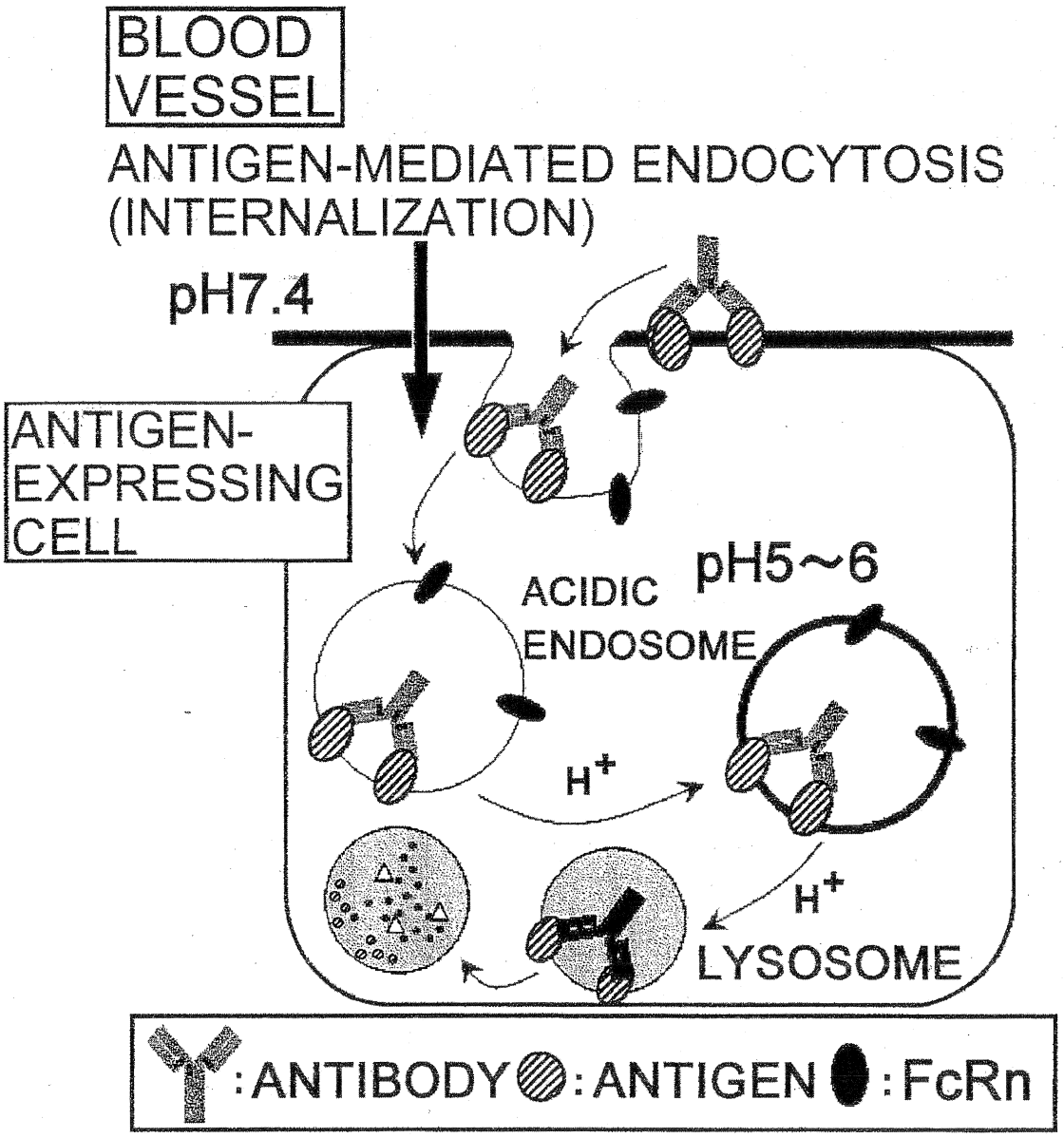

BLOOD VESSEL
ANTIGEN-MEDIATED ENDOCYTOSIS (INTERNALIZATION)
pH7.4
ANTIGEN-EXPRESSING CELL
ACIDIC ENDOSOME
pH5~6
H+
H+
LYSOSOME
: ANTIBODY
: ANTIGEN
: FcRn

FIG. 1

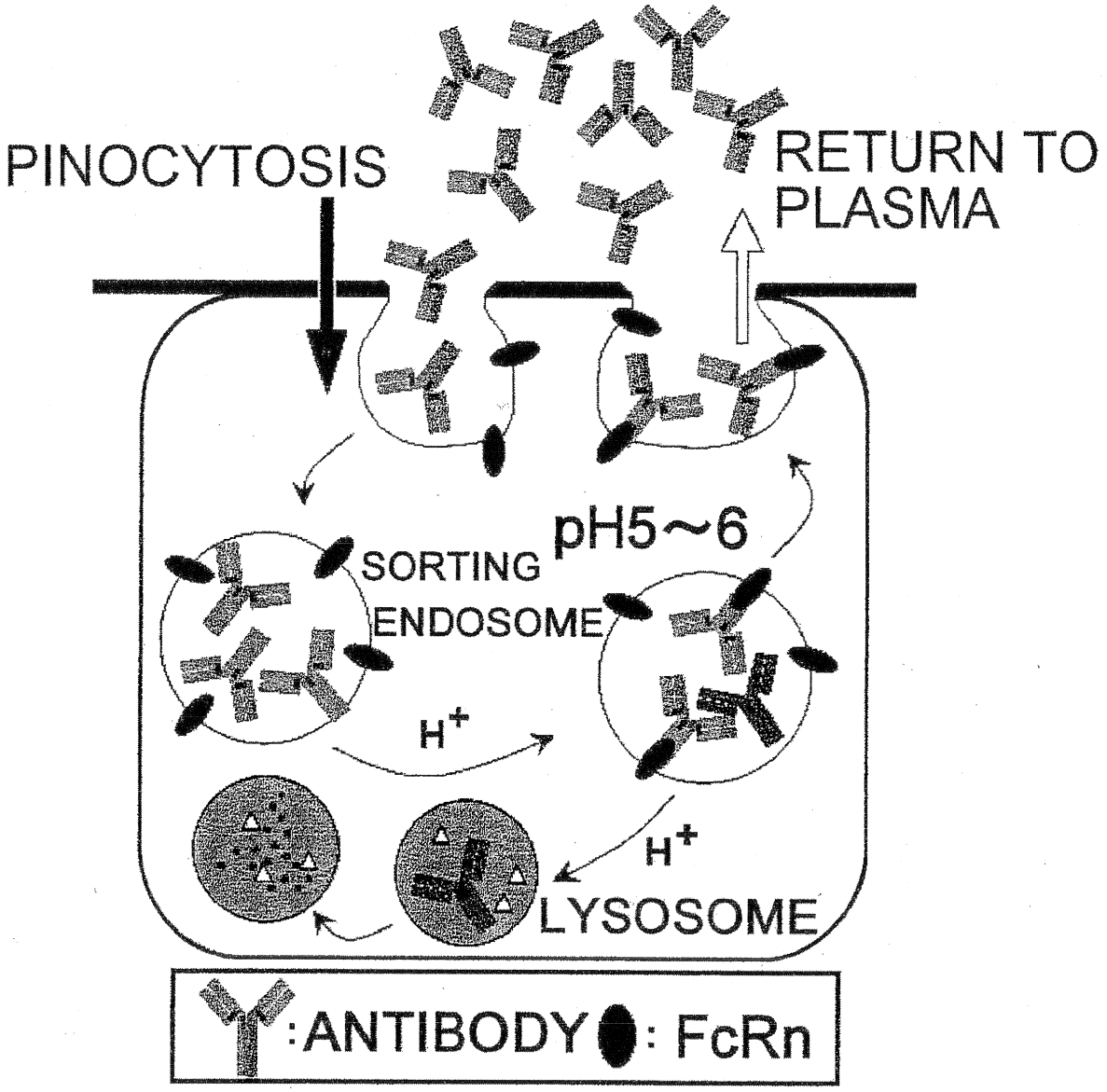

PINOCYTOSIS
RETURN TO PLASMA
pH5~6
SORTING ENDOSOME
H+
H+
LYSOSOME
:ANTIBODY
: FcRn

FIG. 2

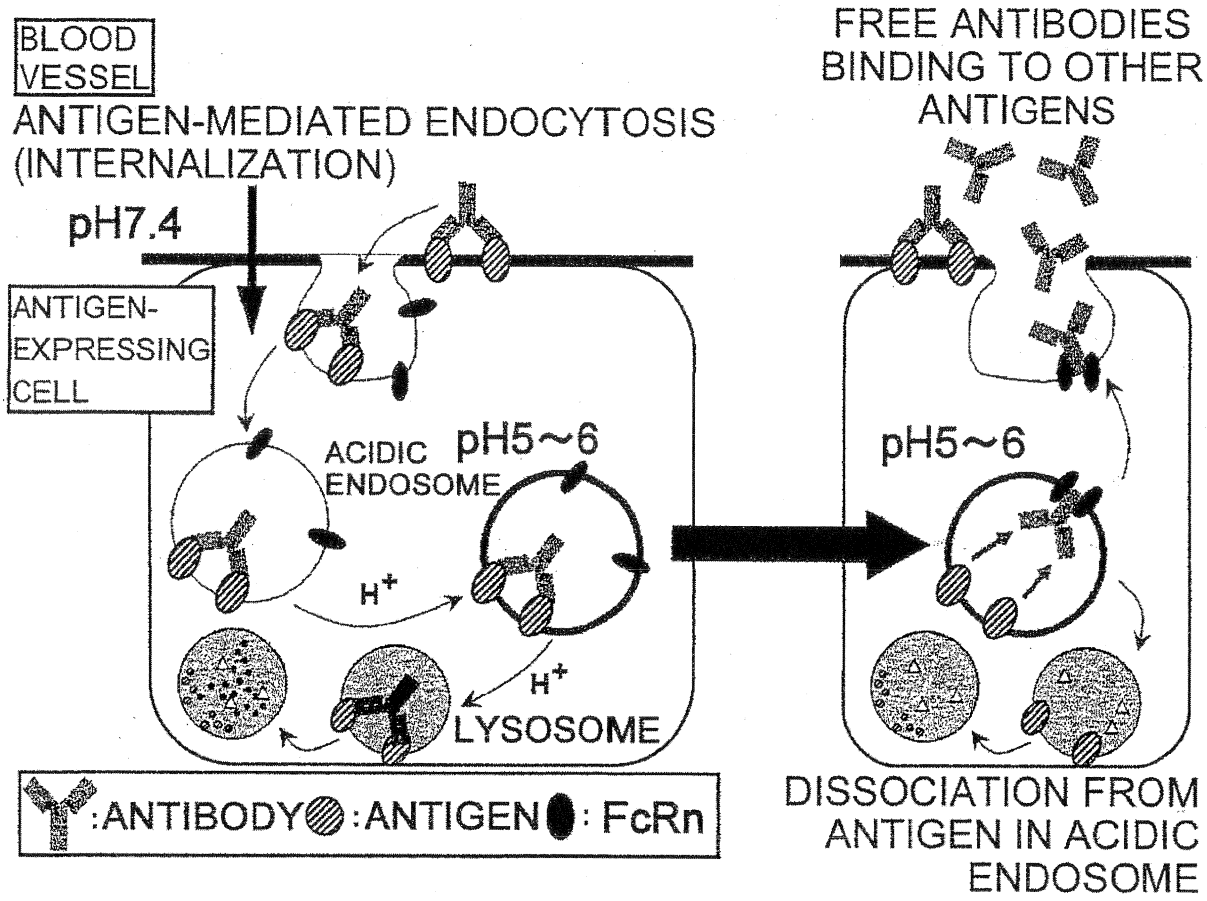

BLOOD VESSEL
ANTIGEN-MEDIATED ENDOCYTOSIS (INTERNALIZATION)
pH7.4
ANTIGEN-EXPRESSING CELL
ACIDIC ENDOSOME
pH5~6
H+
H+
LYSOSOME
:ANTIBODY
:ANTIGEN
: FcRn
FREE ANTIBODIES BINDING TO OTHER ANTIGENS
pH5~6
DISSOCIATION FROM ANTIGEN IN ACIDIC ENDOSOME

FIG. 3

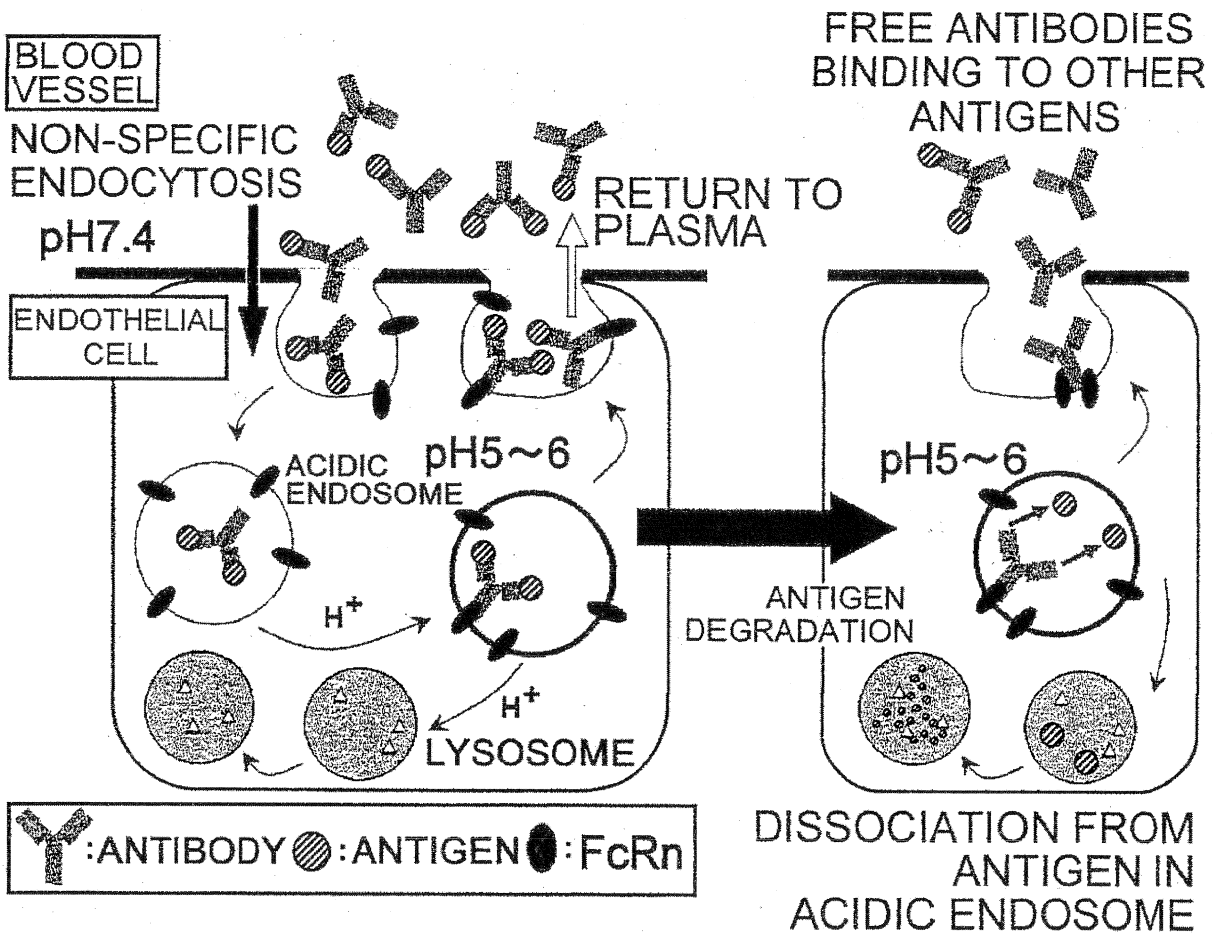

BLOOD VESSEL
NON-SPECIFIC ENDOCYTOSIS
pH7.4
ENDOTHELIAL CELL
RETURN TO PLASMA
FREE ANTIBODIES BINDING TO OTHER ANTIGENS
ACIDIC ENDOSOME
pH5~6
H+
H+
LYSOSOME
ANTIGEN DEGRADATION
pH5~6
:ANTIBODY
:ANTIGEN
:FcRn
DISSOCIATION FROM ANTIGEN IN ACIDIC ENDOSOME

FIG. 4

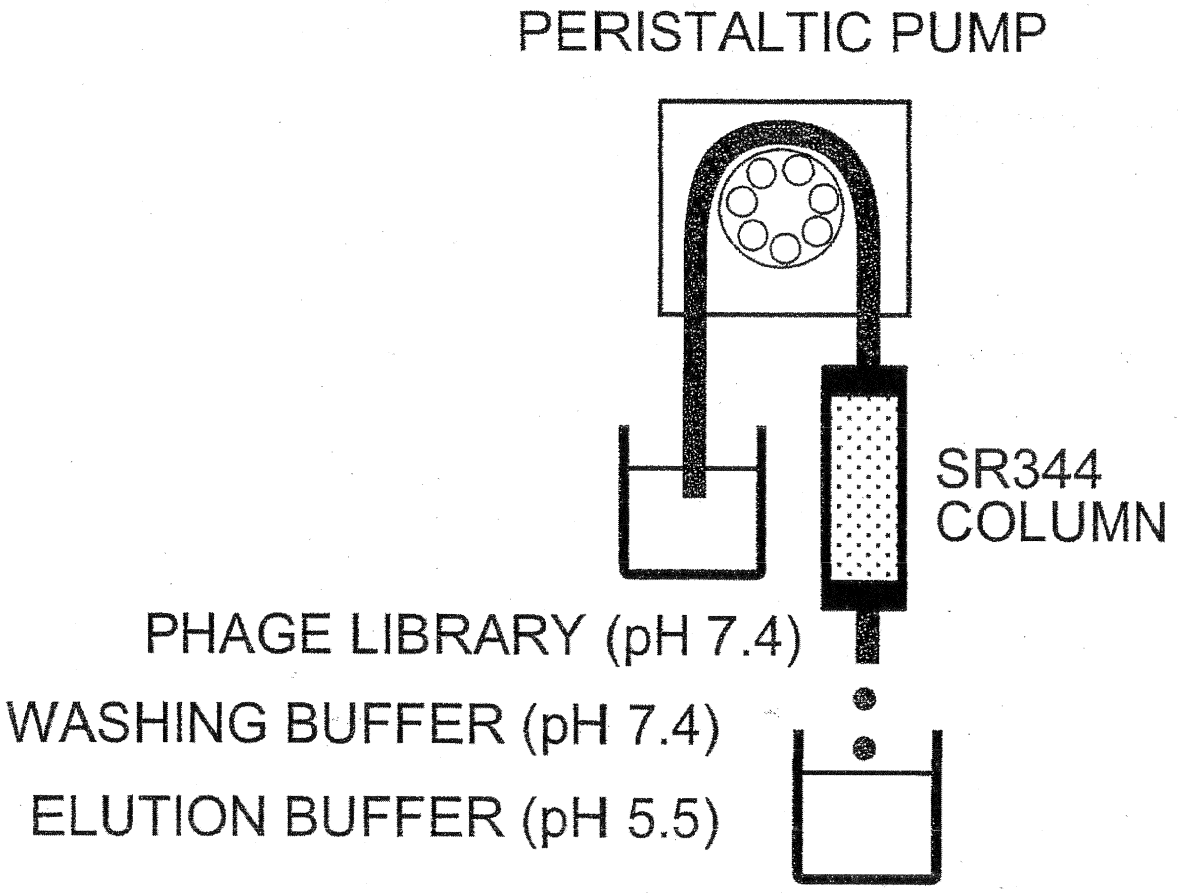

PERISTALTIC PUMP
SR344
COLUMN
PHAGE LIBRARY (pH 7.4)
WASHING BUFFER (pH 7.4)
ELUTION BUFFER (pH 5.5)

FIG. 5

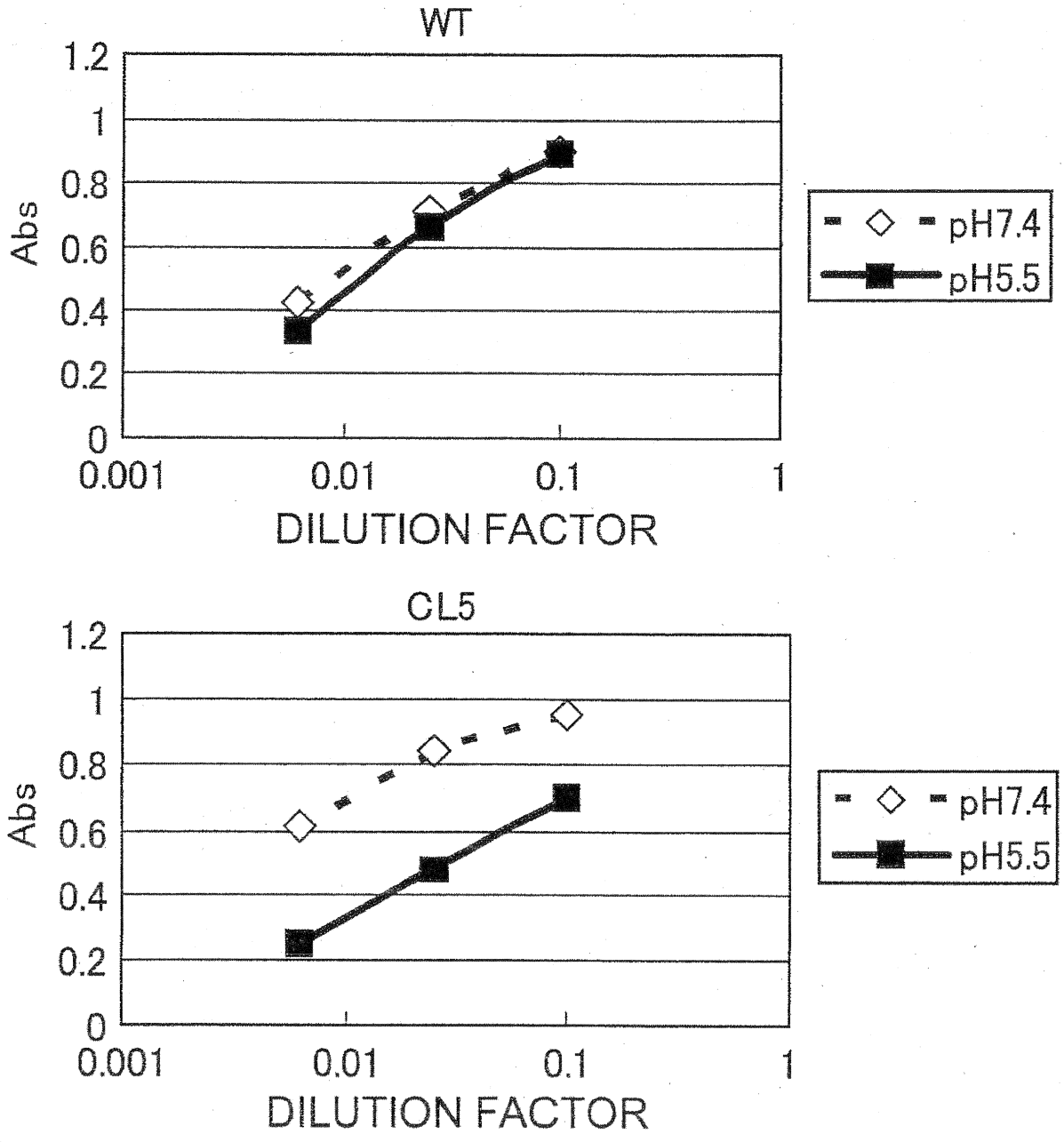

WT
1.2
1
0.8
0.6
0.4
0.2
0
Abs
0.001
0.01
0.1
1
DILUTION FACTOR
pH7.4
pH5.5
CL5
1.2
1
0.8
0.6
0.4
0.2
0
Abs
0.001
0.01
0.1
1
DILUTION FACTOR
pH7.4
pH5.5

FIG. 6

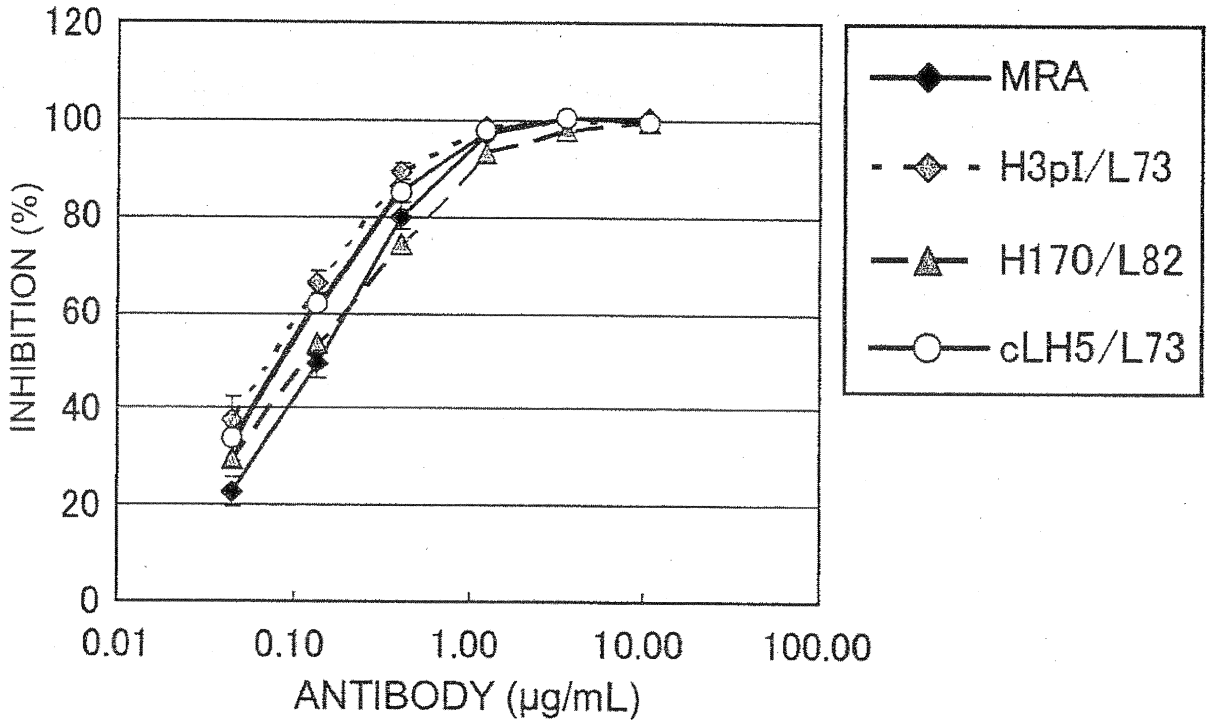

120
100
80
60
40
20
0
INHIBITION (%)
0.01
0.10
1.00
10.00
100.00
ANTIBODY (μg/mL)
MRA
H3pI/L73
H170/L82
cLH5/L73

FIG. 7

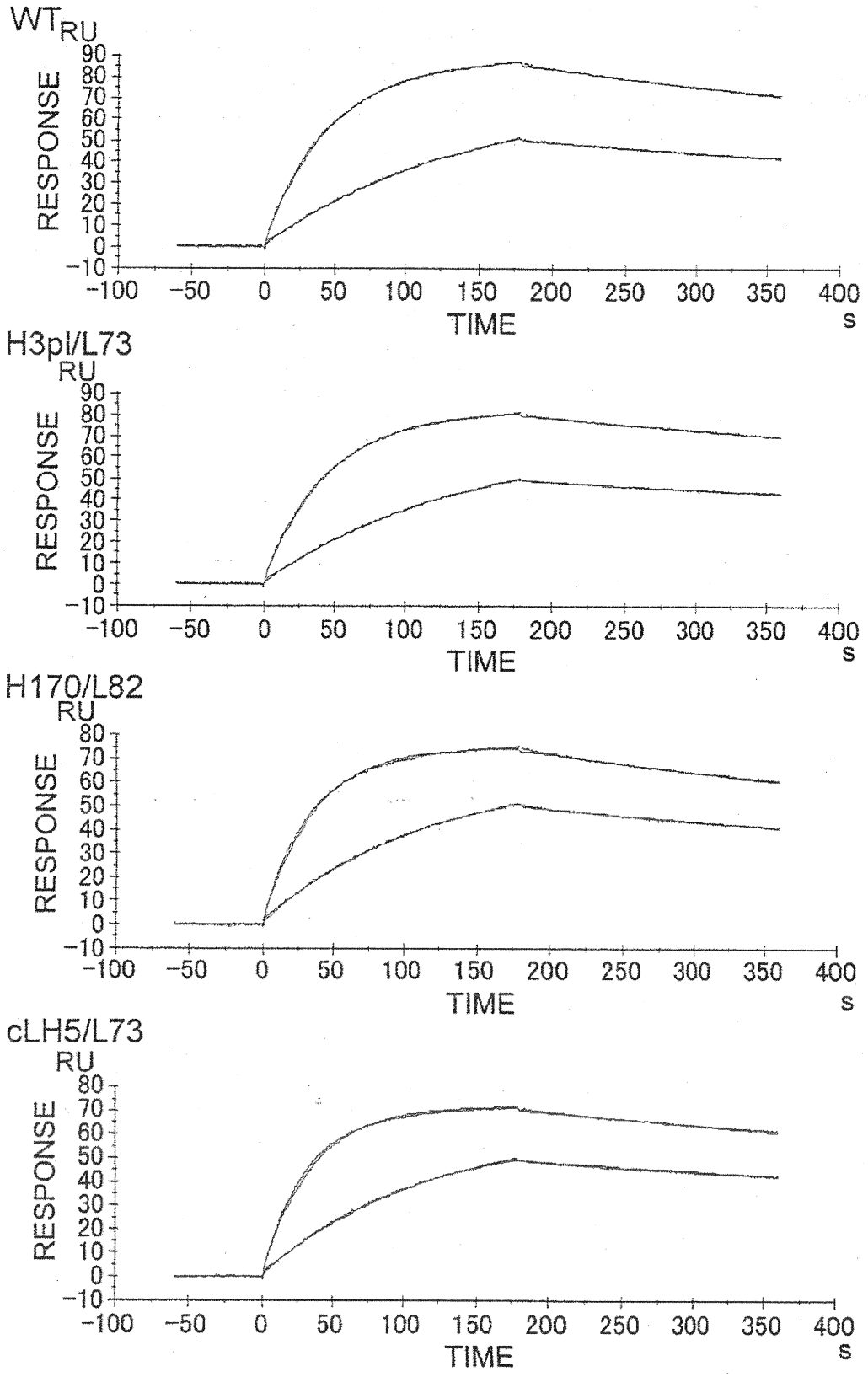

WT
RU
RESPONSE
90
80
70
60
50
40
30
20
10
0
−10
−100
−50
0
50
100
150
200
250
300
350
400
TIME
s
H3pI/L73
RU
RESPONSE
TIME
s
H170/L82
RU
RESPONSE
TIME
s
cLH5/L73
RU
RESPONSE
TIME
s

FIG. 8

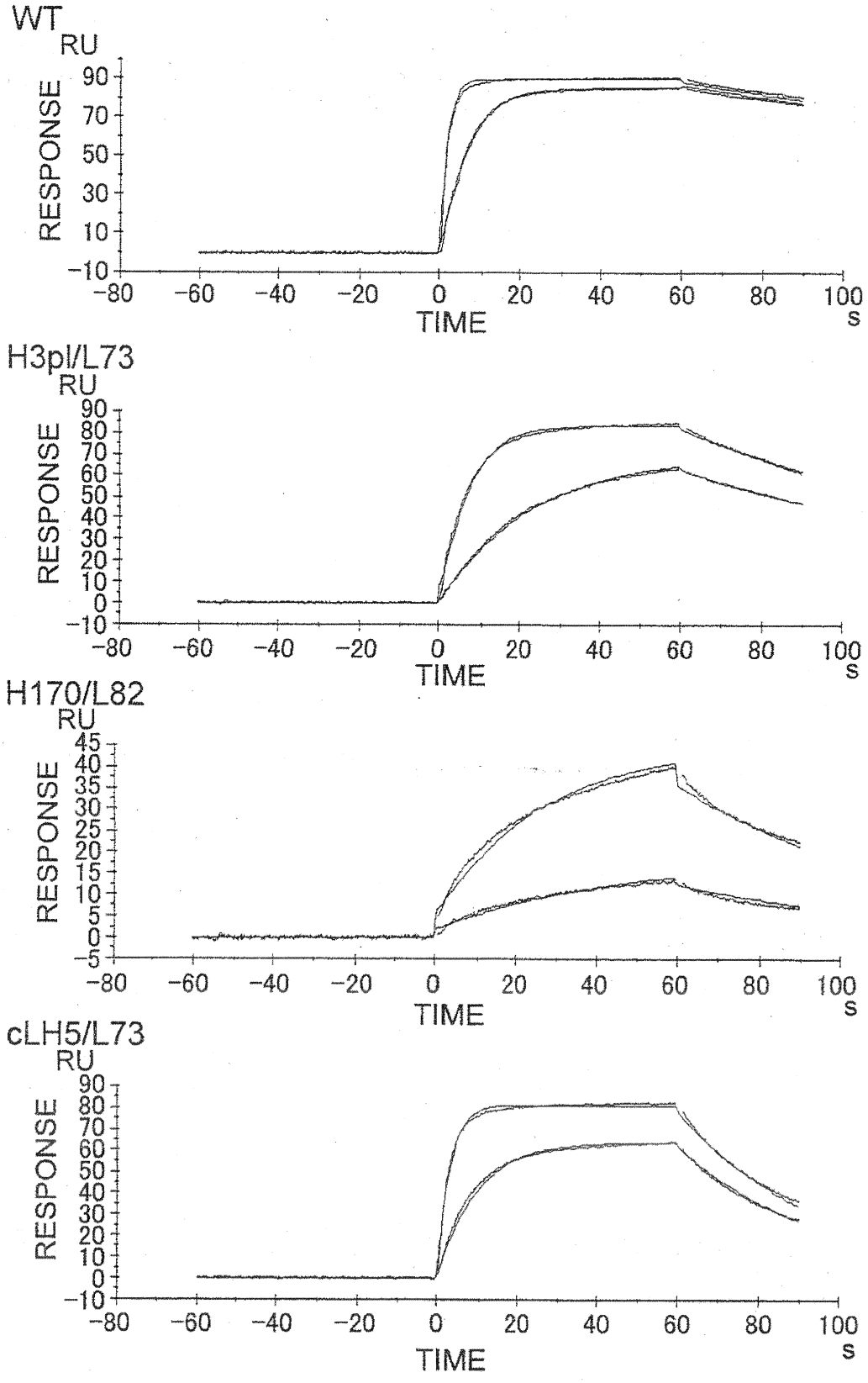

WT
RU
RESPONSE
90
70
50
30
10
−10
−80
−60
−40
−20
0
20
40
60
80
100
TIME
s
H3pl/L73
RU
RESPONSE
90
80
70
60
50
40
30
20
10
0
−10
−80
−60
−40
−20
0
20
40
60
80
100
TIME
s
H170/L82
RU
RESPONSE
45
40
35
30
25
20
15
10
5
0
−5
−80
−60
−40
−20
0
20
40
60
80
100
TIME
s
cLH5/L73
RU
RESPONSE
90
80
70
60
50
40
30
20
10
0
−10
−80
−60
−40
−20
0
20
40
60
80
100
TIME
s

FIG. 9

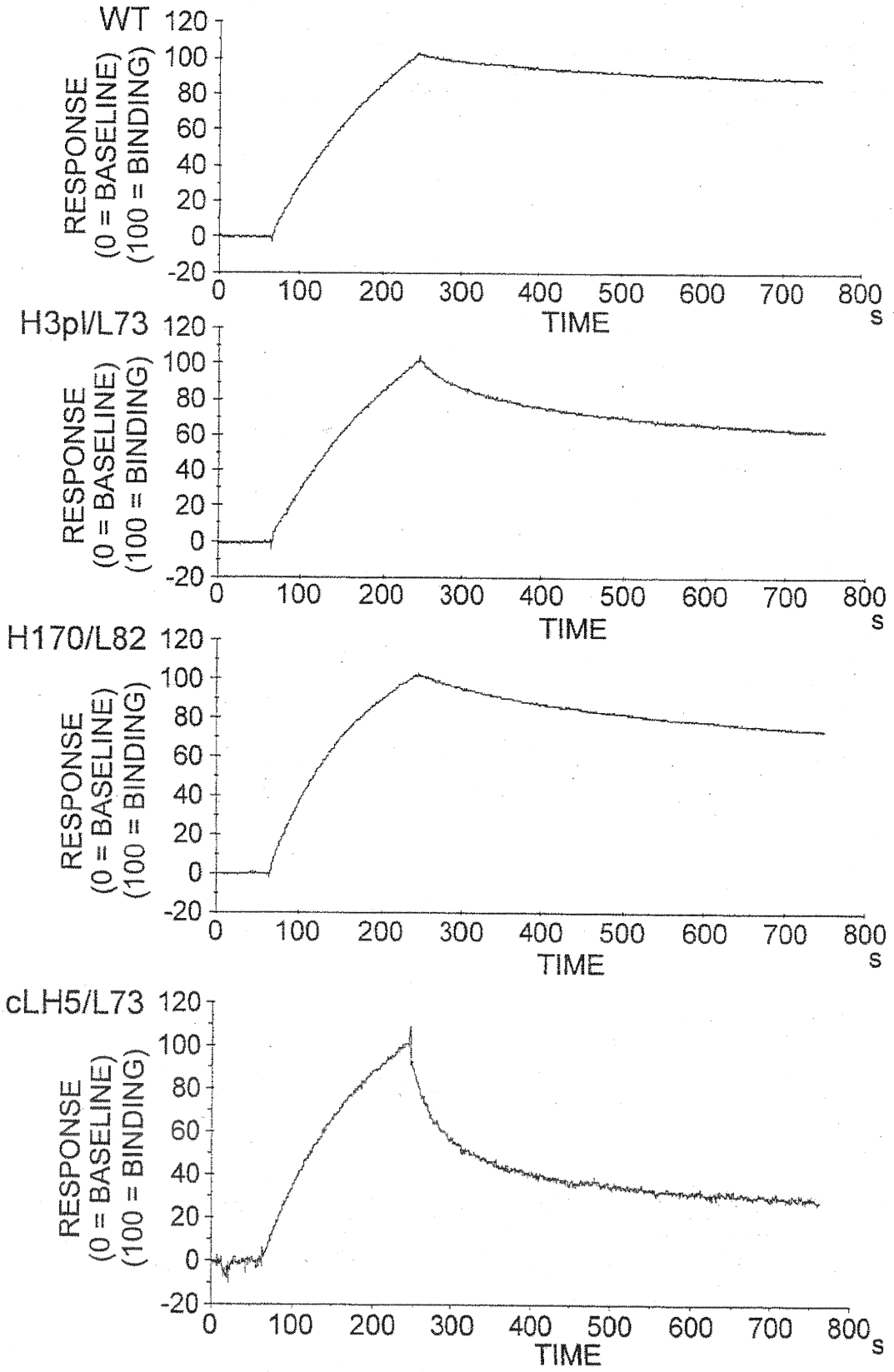

WT
H3pl/L73
H170/L82
cLH5/L73
RESPONSE
(0 = BASELINE)
(100 = BINDING)
120
100
80
60
40
20
0
-20
0
100
200
300
400
500
600
700
800
TIME
s

FIG. 10

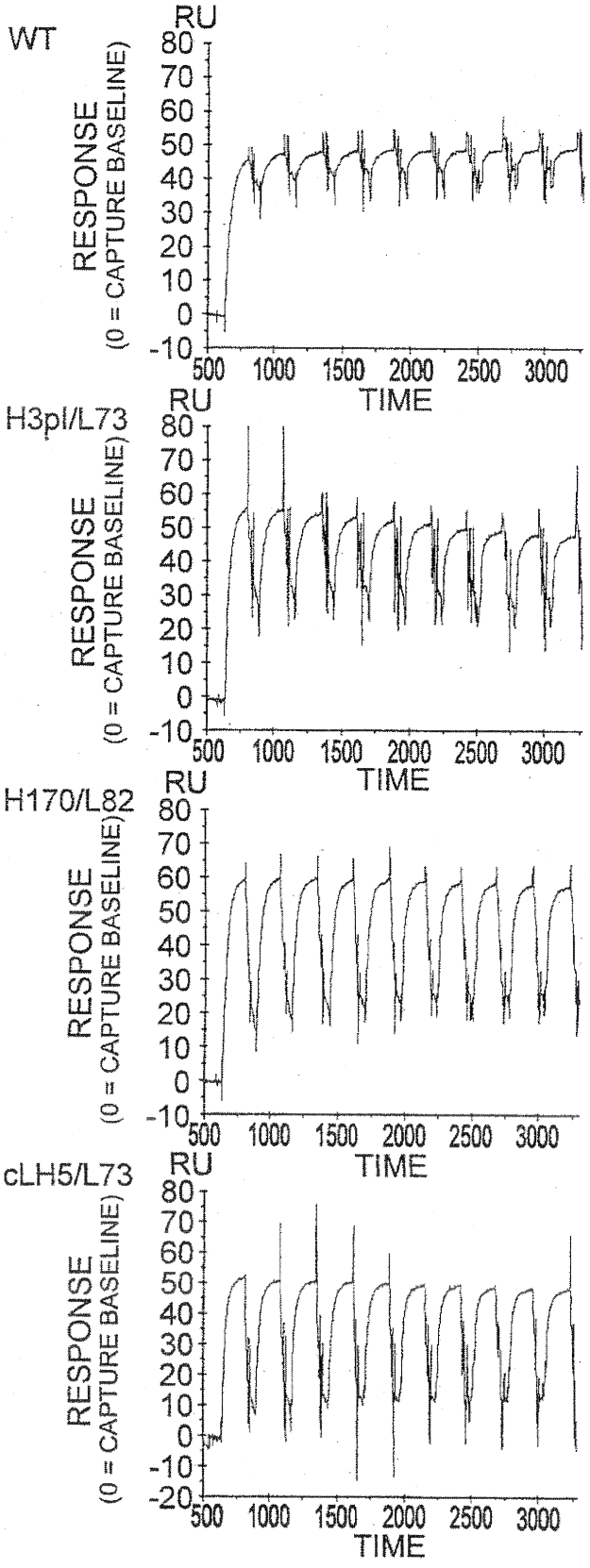

WT
H3pI/L73
H170/L82
cLH5/L73
RU
RESPONSE
(0 = CAPTURE BASELINE)
TIME
80
70
60
50
40
30
20
10
0
-10
-20
500
1000
1500
2000
2500
3000

FIG. 11

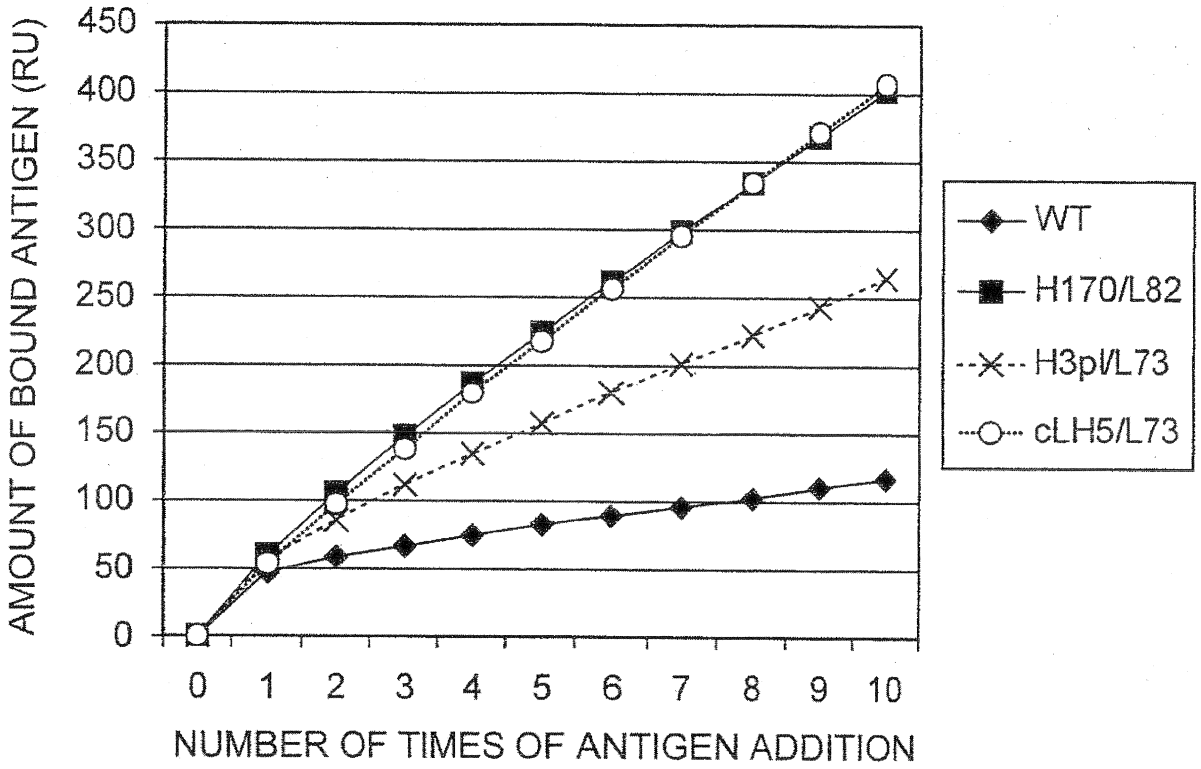

AMOUNT OF BOUND ANTIGEN (RU)
450
400
350
300
250
200
150
100
50
0
0 1 2 3 4 5 6 7 8 9 10
NUMBER OF TIMES OF ANTIGEN ADDITION
WT
H170/L82
H3pI/L73
cLH5/L73

FIG. 12

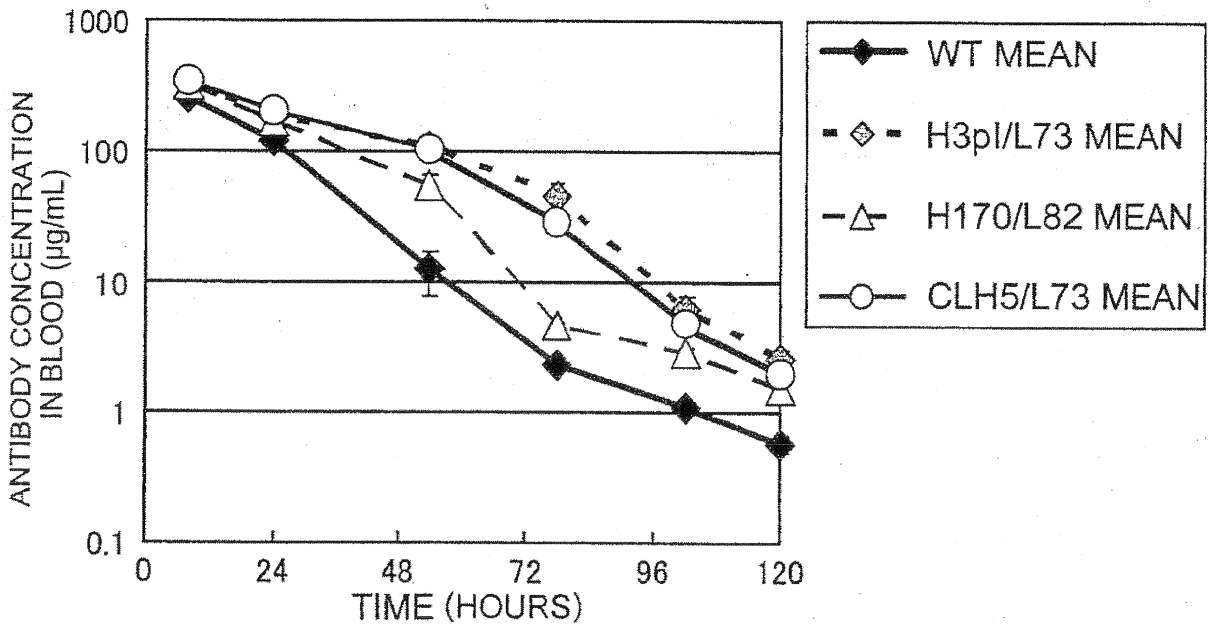

1000
100
10
1
0.1
ANTIBODY CONCENTRATION IN BLOOD (μg/mL)
0
24
48
72
96
120
TIME (HOURS)
WT MEAN
H3pI/L73 MEAN
H170/L82 MEAN
CLH5/L73 MEAN

FIG. 13

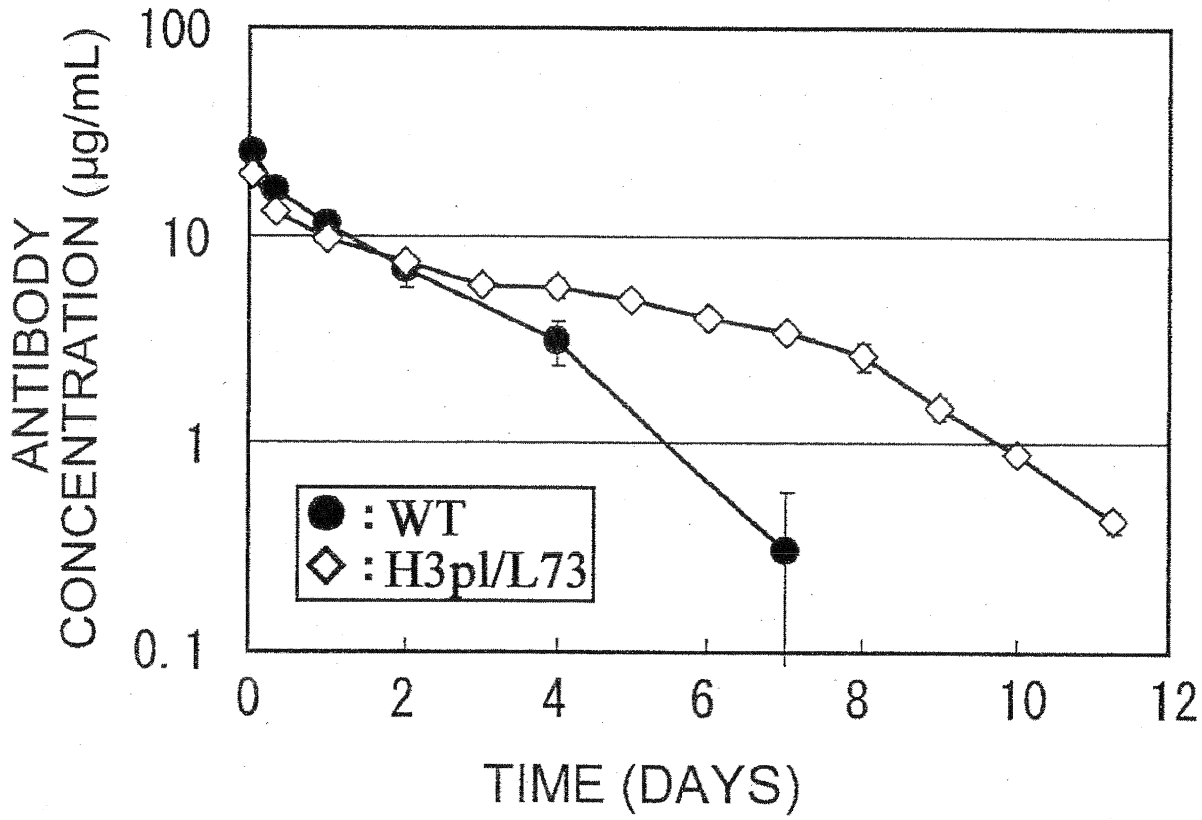

ANTIBODY CONCENTRATION (μg/mL)
100
10
1
0.1
0
2
4
6
8
10
12
TIME (DAYS)
● : WT
◇ : H3pl/L73

FIG. 14

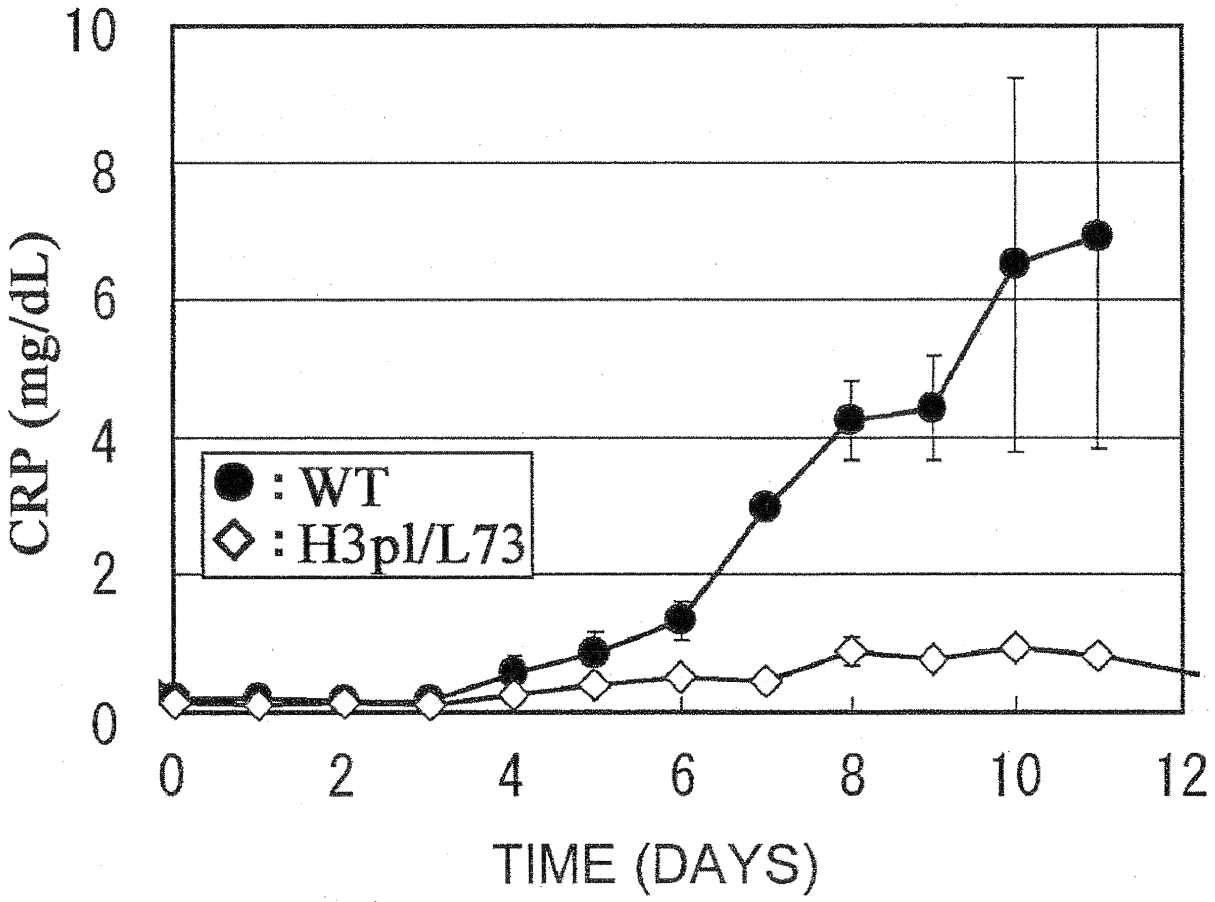


FIG. 15

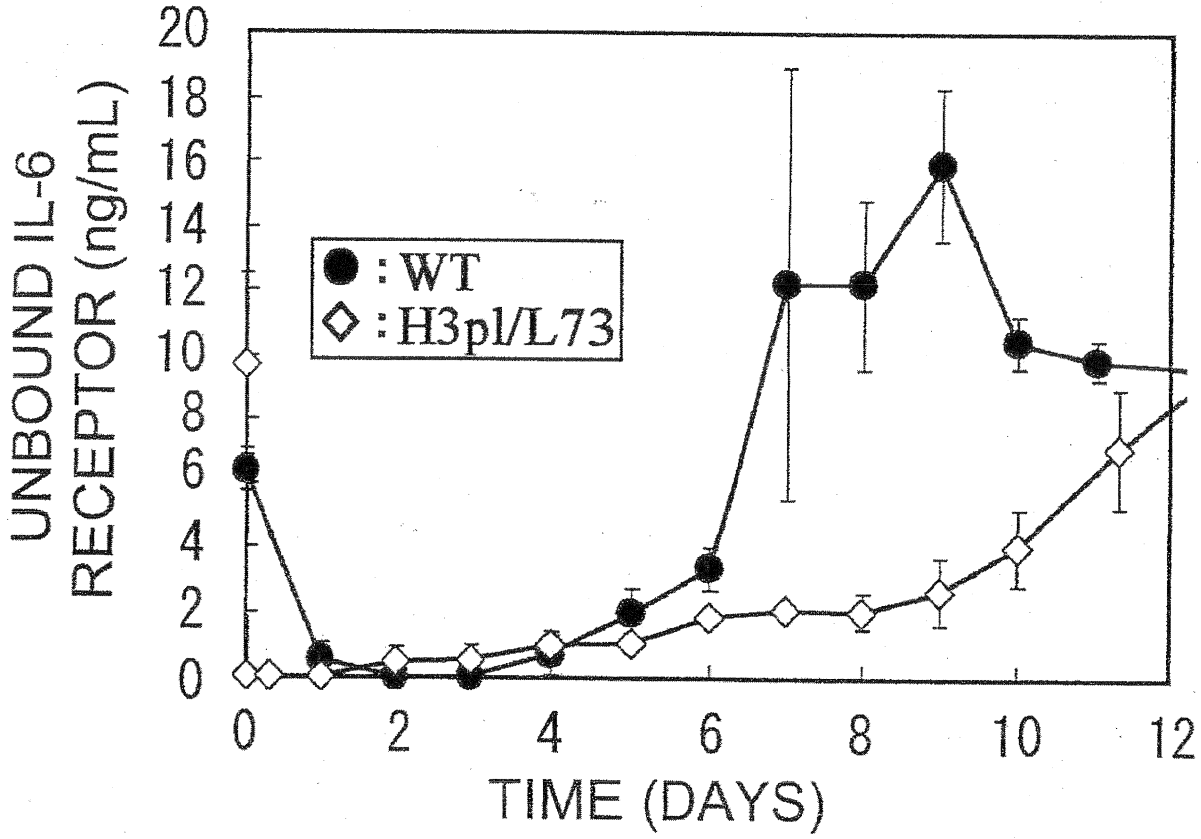

UNBOUND IL-6 RECEPTOR (ng/mL)
20
18
16
14
12
10
8
6
4
2
0
0
2
4
6
8
10
12
TIME (DAYS)
● : WT
◇ : H3pl/L73

FIG. 16

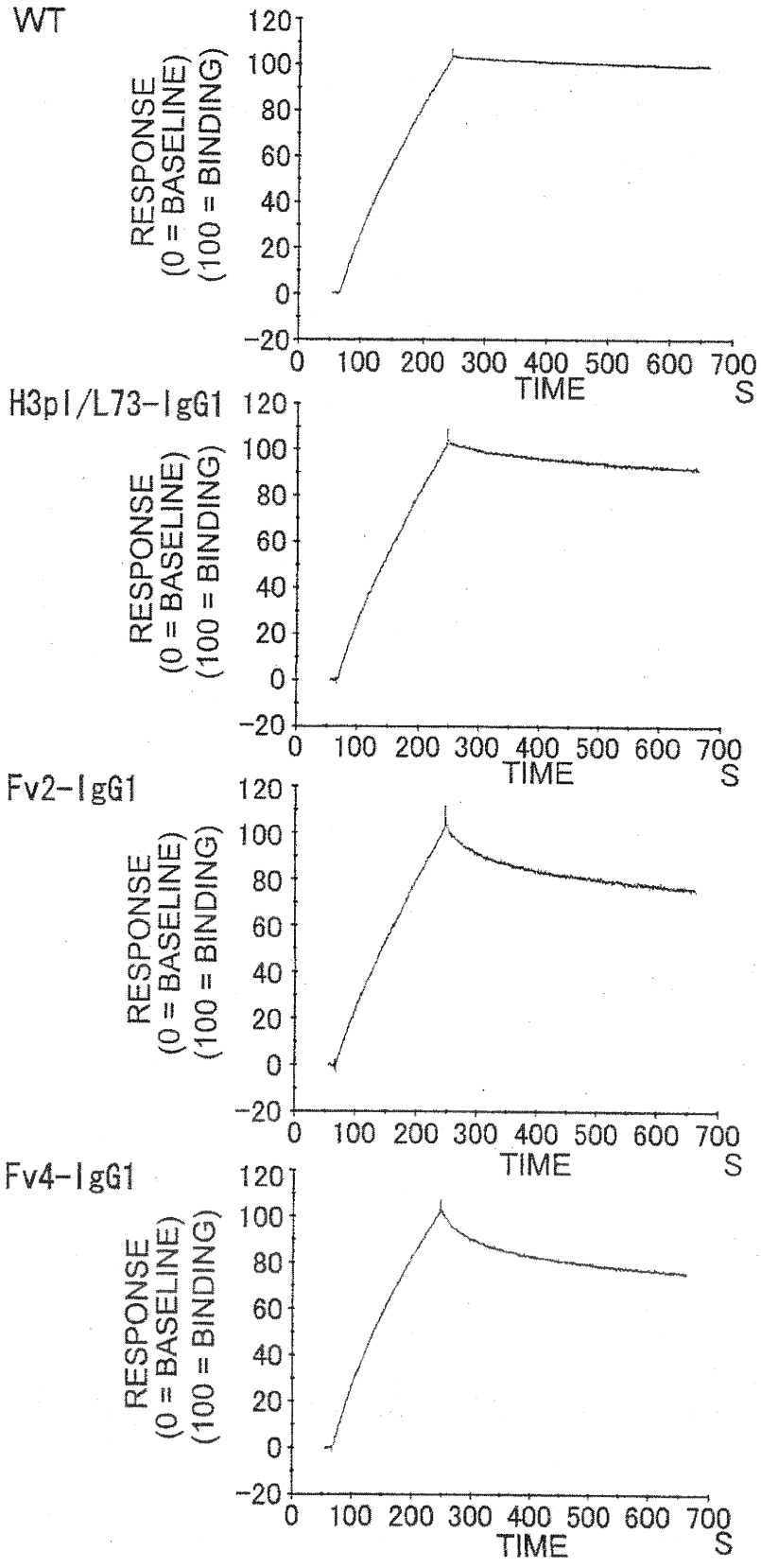

WT
RESPONSE
(0 = BASELINE)
(100 = BINDING)
120
100
80
60
40
20
0
-20
0 100 200 300 400 500 600 700
TIME
S
H3pI/L73-IgG1
RESPONSE
(0 = BASELINE)
(100 = BINDING)
120
100
80
60
40
20
0
-20
0 100 200 300 400 500 600 700
TIME
S
Fv2-IgG1
RESPONSE
(0 = BASELINE)
(100 = BINDING)
120
100
80
60
40
20
0
-20
0 100 200 300 400 500 600 700
TIME
S
Fv4-IgG1
RESPONSE
(0 = BASELINE)
(100 = BINDING)
120
100
80
60
40
20
0
-20
0 100 200 300 400 500 600 700
TIME
S

FIG. 17

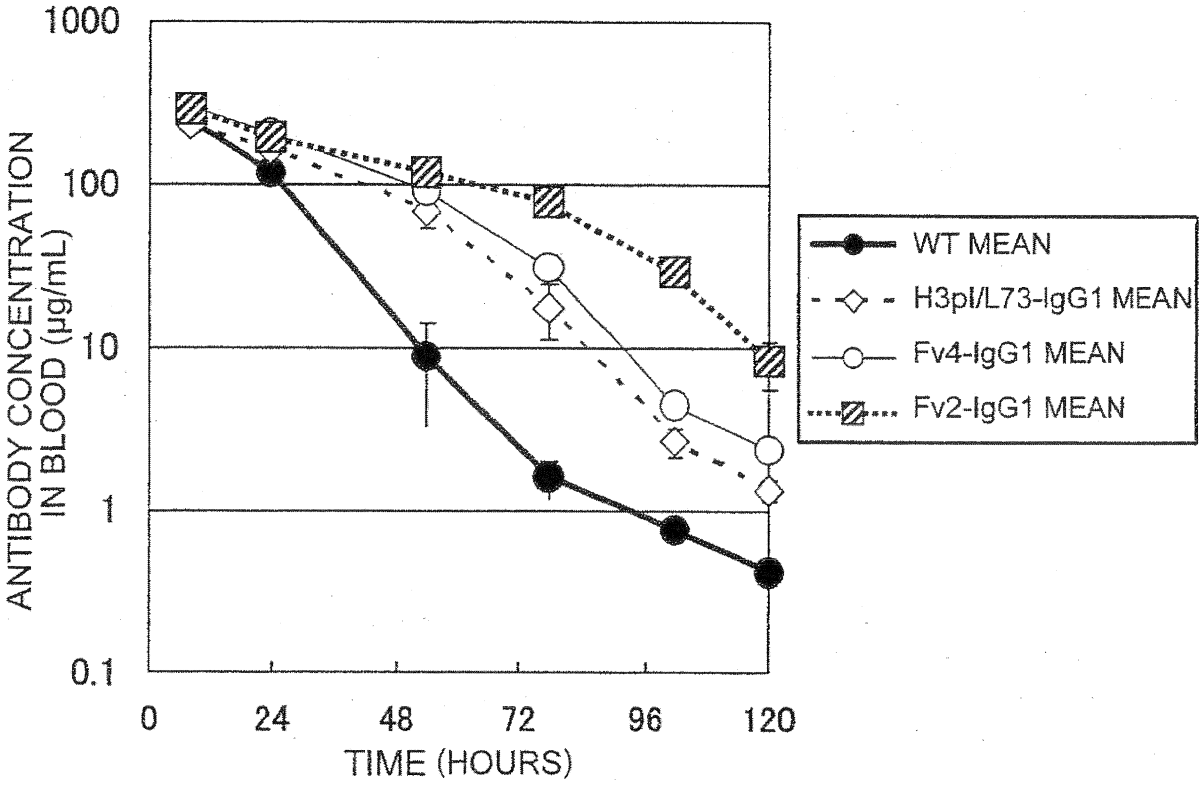

1000
100
10
1
0.1
ANTIBODY CONCENTRATION IN BLOOD (μg/mL)
0
24
48
72
96
120
TIME (HOURS)
WT MEAN
H3pI/L73-IgG1 MEAN
Fv4-IgG1 MEAN
Fv2-IgG1 MEAN

FIG. 18

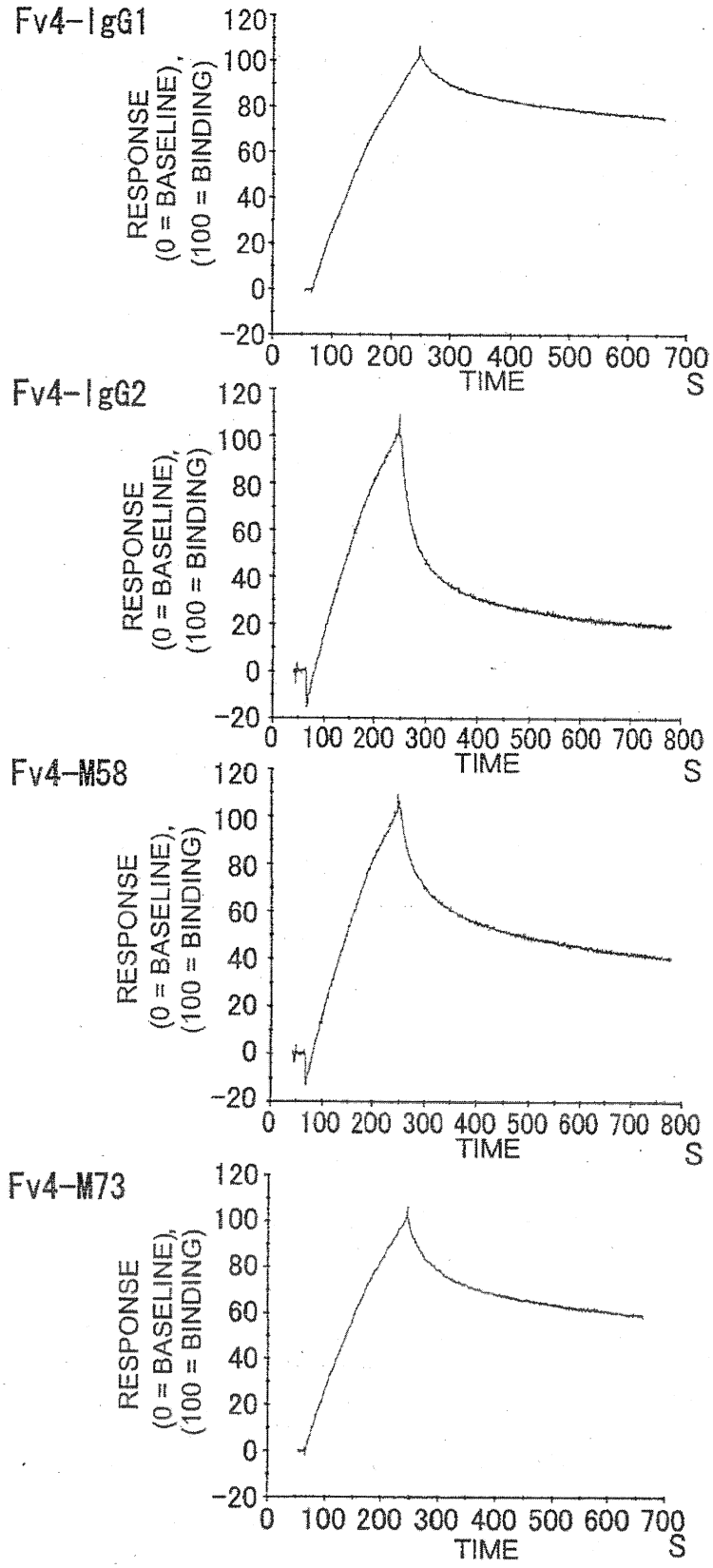

Fv4-IgG1
RESPONSE
(0 = BASELINE),
(100 = BINDING)
120
100
80
60
40
20
0
-20
0 100 200 300 400 500 600 700
TIME
S
Fv4-IgG2
RESPONSE
(0 = BASELINE),
(100 = BINDING)
120
100
80
60
40
20
0
-20
0 100 200 300 400 500 600 700 800
TIME
S
Fv4-M58
RESPONSE
(0 = BASELINE),
(100 = BINDING)
120
100
80
60
40
20
0
-20
0 100 200 300 400 500 600 700 800
TIME
S
Fv4-M73
RESPONSE
(0 = BASELINE),
(100 = BINDING)
120
100
80
60
40
20
0
-20
0 100 200 300 400 500 600 700
TIME
S

FIG. 19

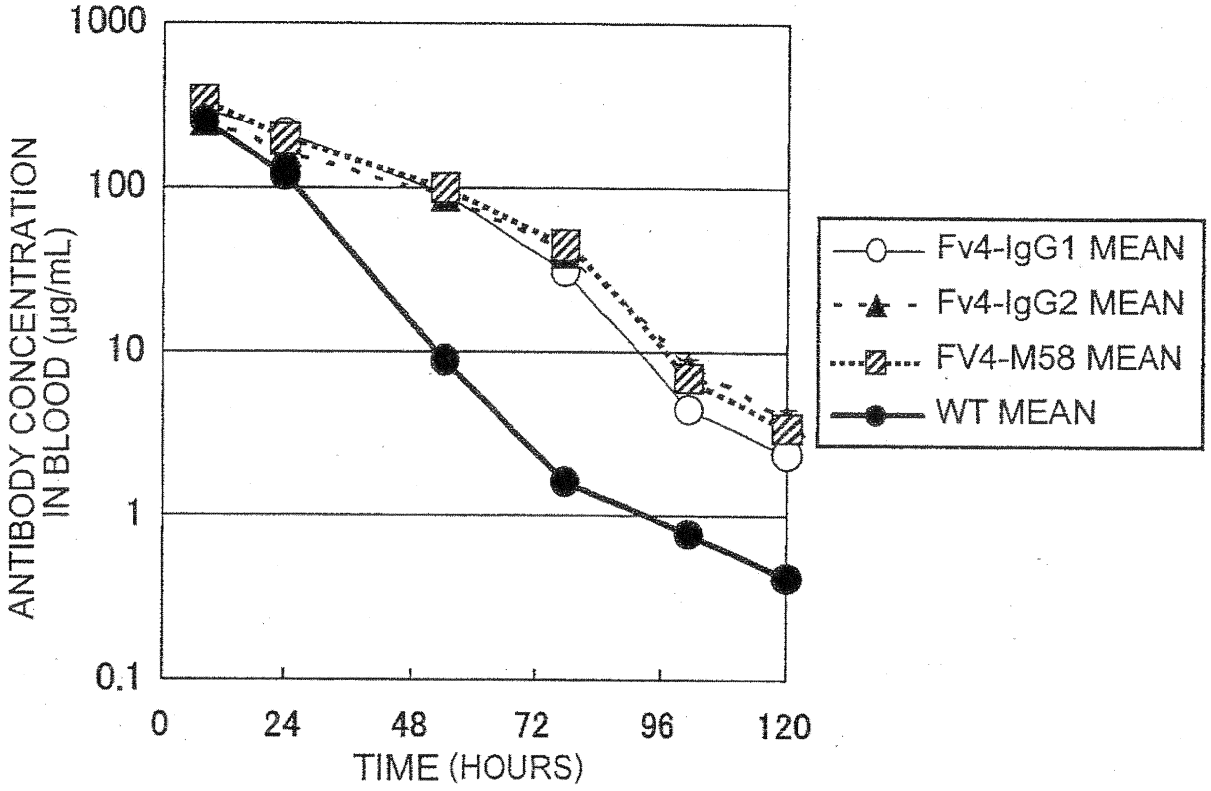

1000
100
10
1
0.1
ANTIBODY CONCENTRATION IN BLOOD (μg/mL)
0
24
48
72
96
120
TIME (HOURS)
Fv4-IgG1 MEAN
Fv4-IgG2 MEAN
FV4-M58 MEAN
WT MEAN

FIG. 20

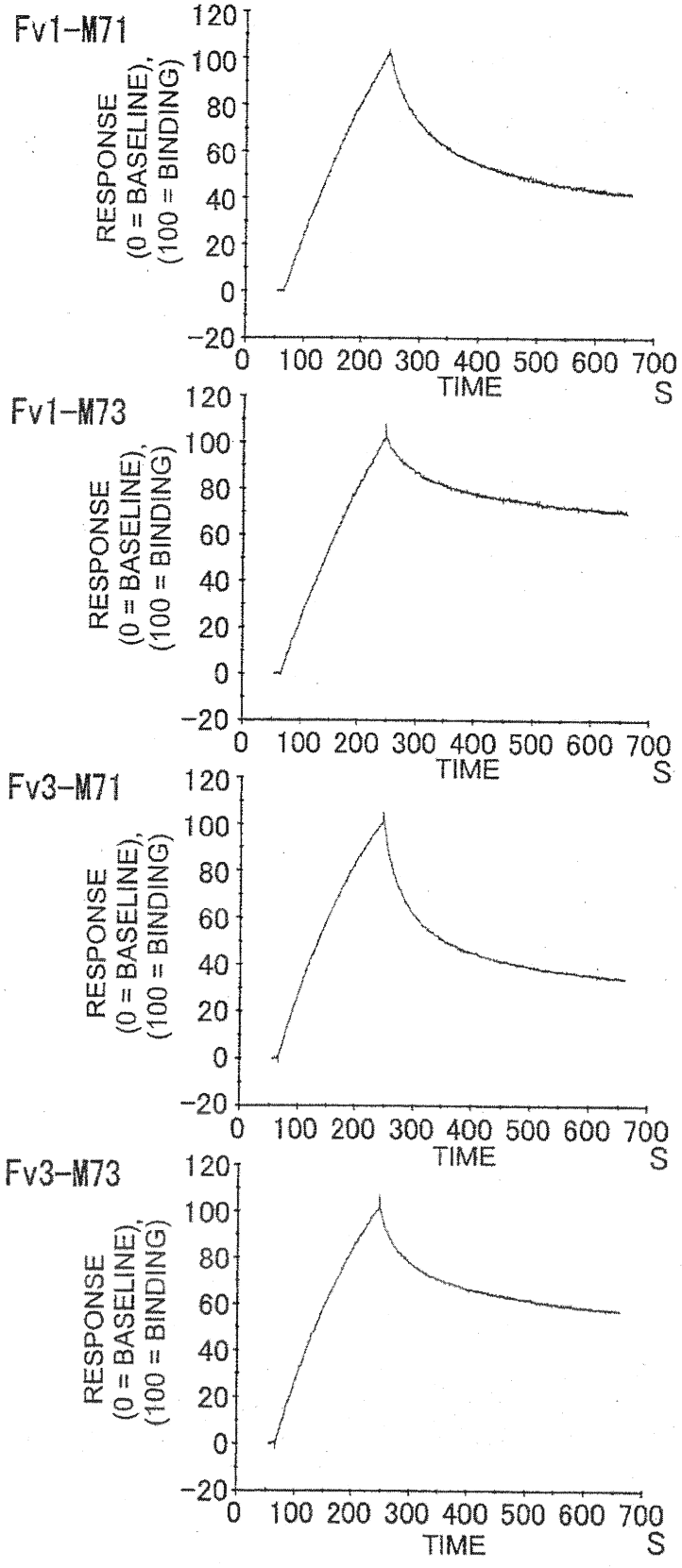

Fv1-M71
RESPONSE
(0 = BASELINE),
(100 = BINDING)
120
100
80
60
40
20
0
-20
0 100 200 300 400 500 600 700
TIME
S
Fv1-M73
RESPONSE
(0 = BASELINE),
(100 = BINDING)
120
100
80
60
40
20
0
-20
0 100 200 300 400 500 600 700
TIME
S
Fv3-M71
RESPONSE
(0 = BASELINE),
(100 = BINDING)
120
100
80
60
40
20
0
-20
0 100 200 300 400 500 600 700
TIME
S
Fv3-M73
RESPONSE
(0 = BASELINE),
(100 = BINDING)
120
100
80
60
40
20
0
-20
0 100 200 300 400 500 600 700
TIME
S

FIG. 21

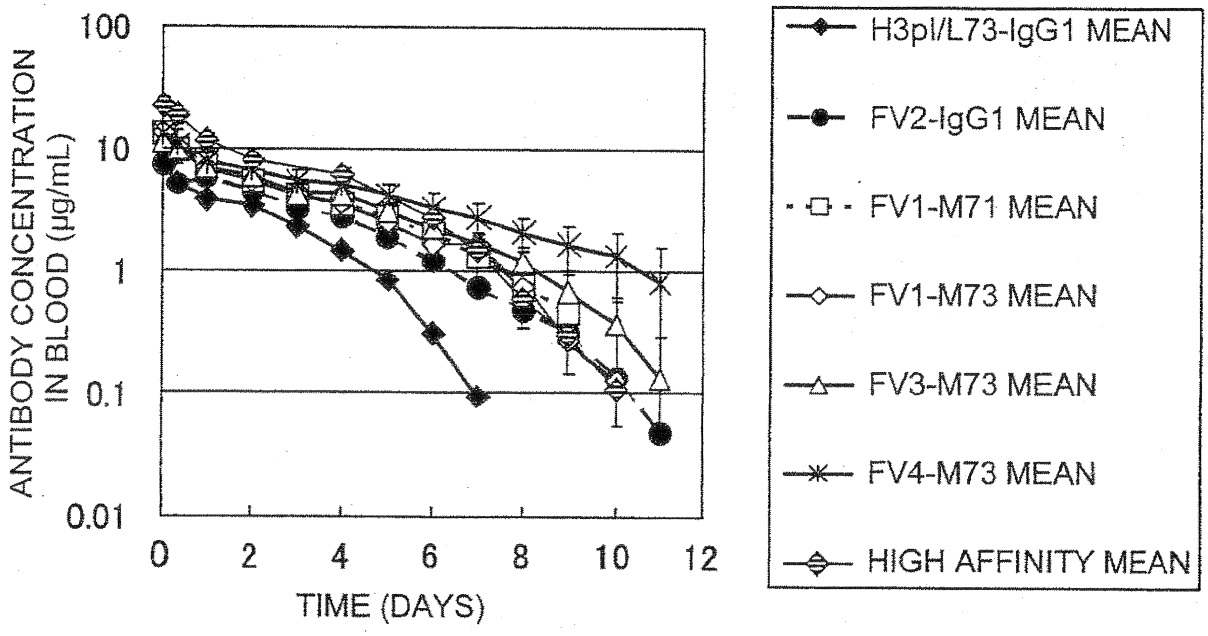

100
10
1
0.1
0.01
ANTIBODY CONCENTRATION IN BLOOD (μg/mL)
0
2
4
6
8
10
12
TIME (DAYS)
H3pI/L73-IgG1 MEAN
FV2-IgG1 MEAN
FV1-M71 MEAN
FV1-M73 MEAN
FV3-M73 MEAN
FV4-M73 MEAN
HIGH AFFINITY MEAN

FIG. 22

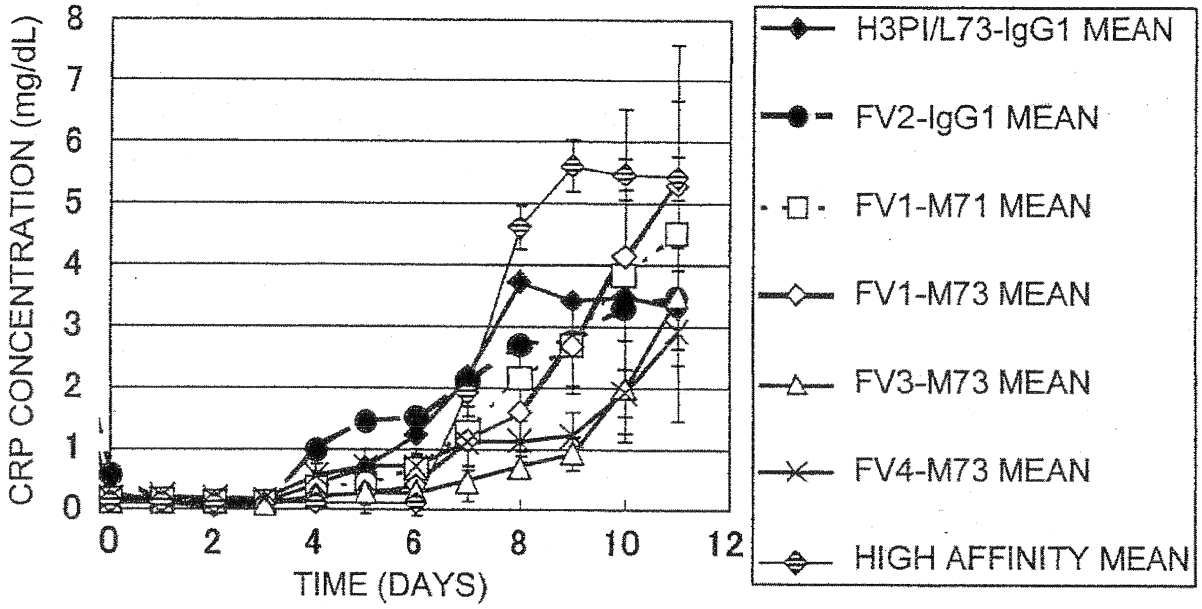

CRP CONCENTRATION (mg/dL)
8
7
6
5
4
3
2
1
0
0
2
4
6
8
10
12
TIME (DAYS)
H3PI/L73-IgG1 MEAN
FV2-IgG1 MEAN
FV1-M71 MEAN
FV1-M73 MEAN
FV3-M73 MEAN
FV4-M73 MEAN
HIGH AFFINITY MEAN

FIG. 23

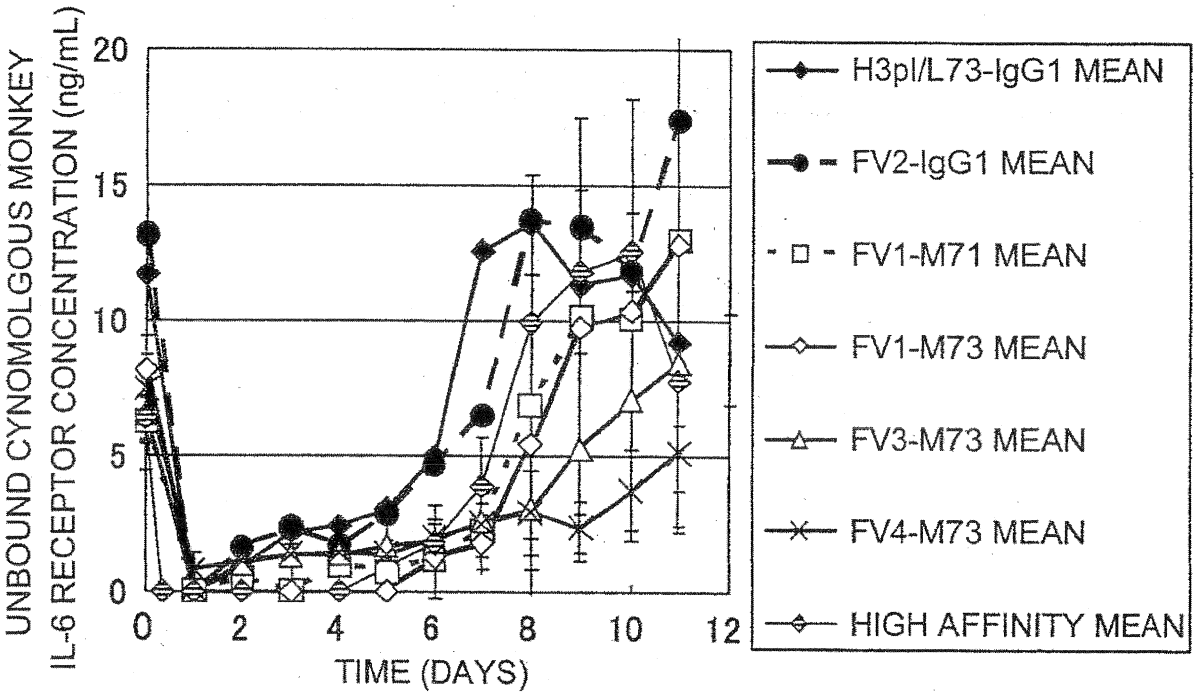

UNBOUND CYNOMOLGOUS MONKEY IL-6 RECEPTOR CONCENTRATION (ng/mL)
20
15
10
5
0
0
2
4
6
8
10
12
TIME (DAYS)
H3pI/L73-IgG1 MEAN
FV2-IgG1 MEAN
FV1-M71 MEAN
FV1-M73 MEAN
FV3-M73 MEAN
FV4-M73 MEAN
HIGH AFFINITY MEAN

FIG. 24

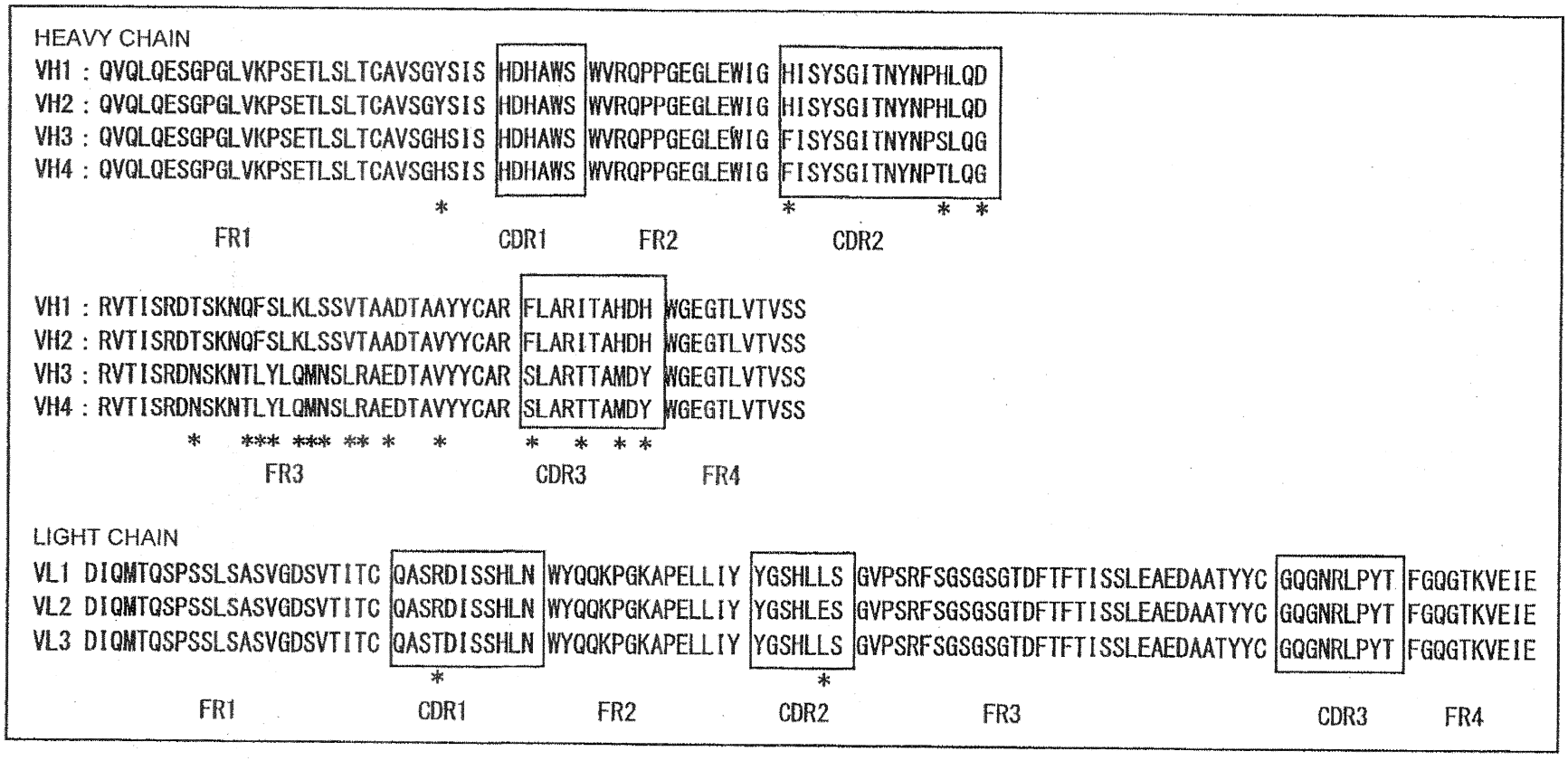

HEAVY CHAIN
VH1 : QVQLQESGPGLVKPSETLSLTCAVSGYSIS HDHAWS WVRQPPGEGLEWIG HISYSGITNYNPHLQD
VH2 : QVQLQESGPGLVKPSETLSLTCAVSGYSIS HDHAWS WVRQPPGEGLEWIG HISYSGITNYNPHLQD
VH3 : QVQLQESGPGLVKPSETLSLTCAVSGHSIS HDHAWS WVRQPPGEGLEWIG FISYSGITNYNPSLQG
VH4 : QVQLQESGPGLVKPSETLSLTCAVSGHSIS HDHAWS WVRQPPGEGLEWIG FISYSGITNYNPTLQG
FR1
CDR1
FR2
CDR2
VH1 : RVTISRDTSKNQFSLKLSSVTAADTAAYYCAR FLARITAHDH WGEGTLVTVSS
VH2 : RVTISRDTSKNQFSLKLSSVTAADTAVYYCAR FLARITAHDH WGEGTLVTVSS
VH3 : RVTISRDNSKNTLYLQMNSLRAEDTAVYYCAR SLARTTAMDY WGEGTLVTVSS
VH4 : RVTISRDNSKNTLYLQMNSLRAEDTAVYYCAR SLARTTAMDY WGEGTLVTVSS
FR3
CDR3
FR4
LIGHT CHAIN
VL1 DIQMTQSPSSLSASVGDSVTITC QASRDISSHLN WYQQKPGKAPELLIY YGSHLLS GVPSRFSGSGSGTDFTFTISSLEAEDAATYYC GQGNRLPYT FGQGTKVEIE
VL2 DIQMTQSPSSLSASVGDSVTITC QASRDISSHLN WYQQKPGKAPELLIY YGSHLES GVPSRFSGSGSGTDFTFTISSLEAEDAATYYC GQGNRLPYT FGQGTKVEIE
VL3 DIQMTQSPSSLSASVGDSVTITC QASTDISSHLN WYQQKPGKAPELLIY YGSHLLS GVPSRFSGSGSGTDFTFTISSLEAEDAATYYC GQGNRLPYT FGQGTKVEIE
FR1
CDR1
FR2
CDR2
FR3
CDR3
FR4

FIG. 25

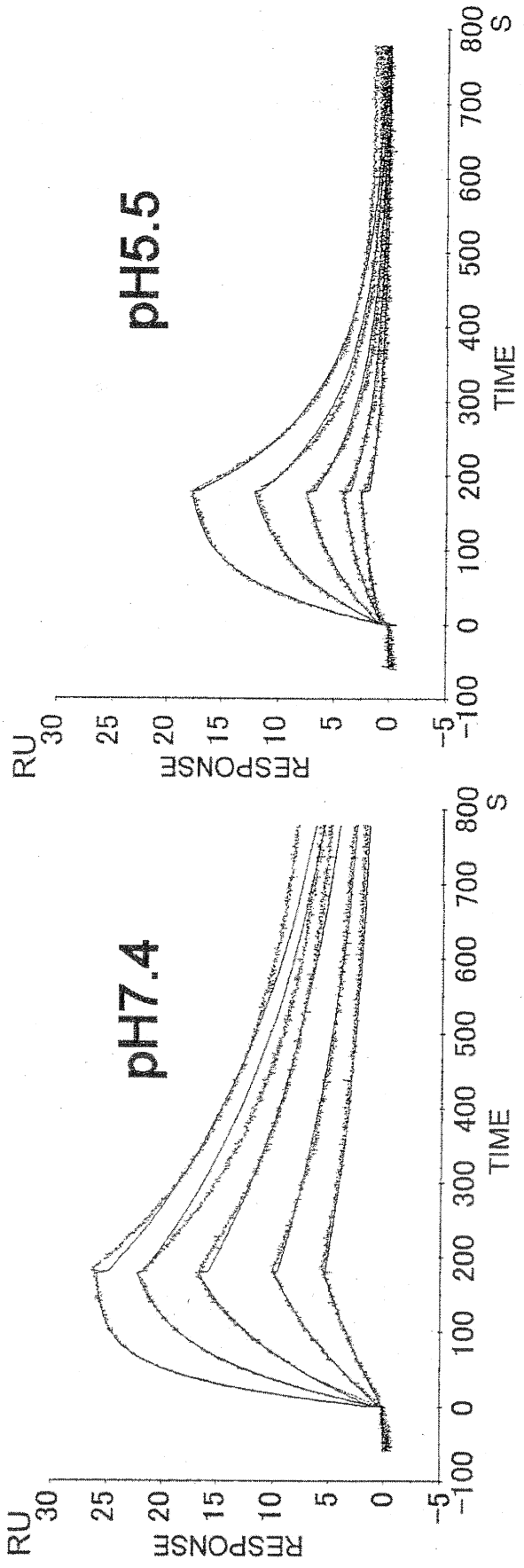
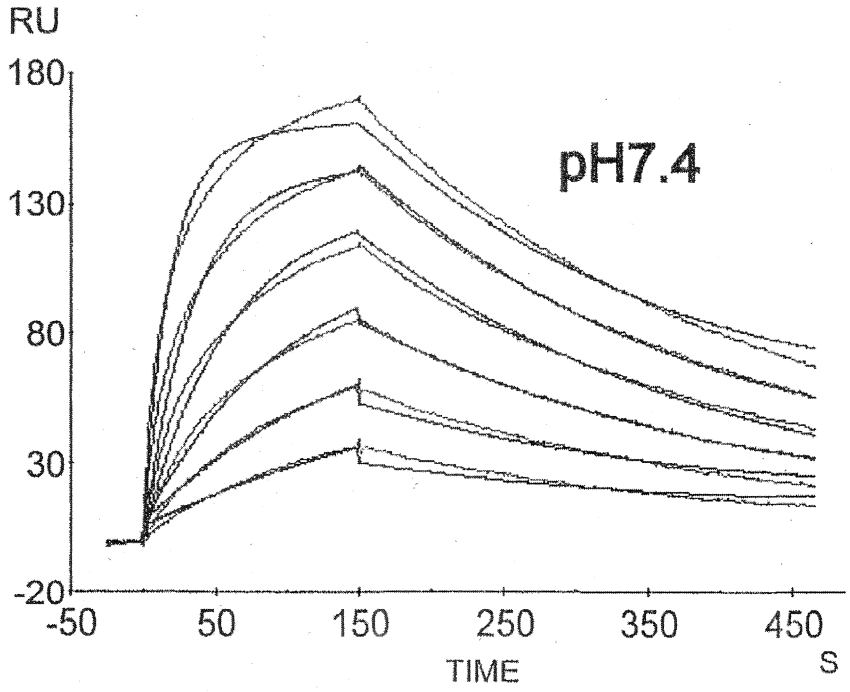

pH5.5
pH7.4
RU
RESPONSE
TIME
S
30
25
20
15
10
5
0
−5
−100
0
100
200
300
400
500
600
700
800

FIG. 26


RU
180
130
80
30
-20
pH7.4
-50
50
150
250
350
450
TIME
S

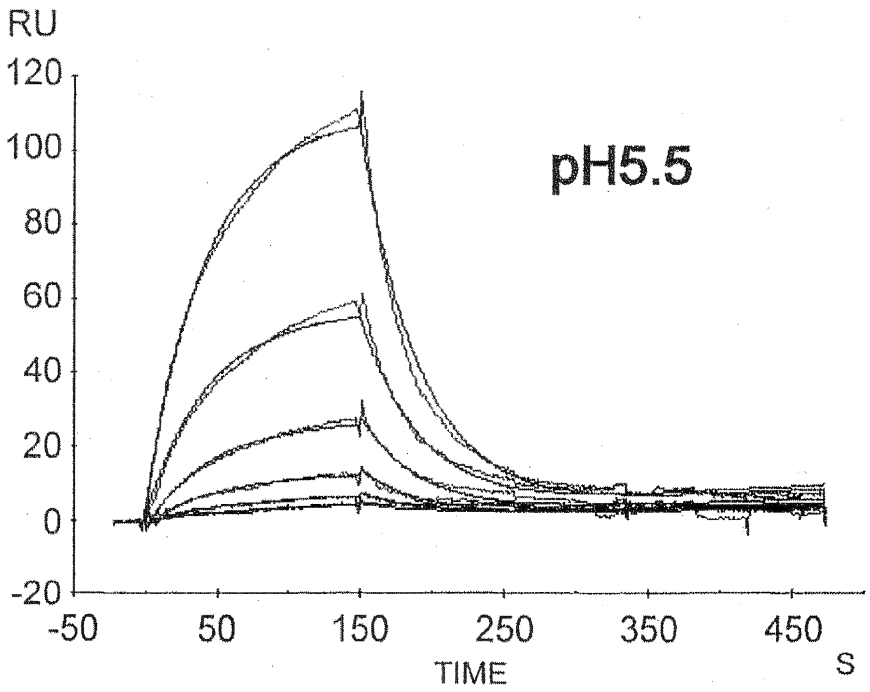

RU
120
100
80
60
40
20
0
-20
pH5.5
-50
50
150
250
350
450
TIME
S

FIG. 27

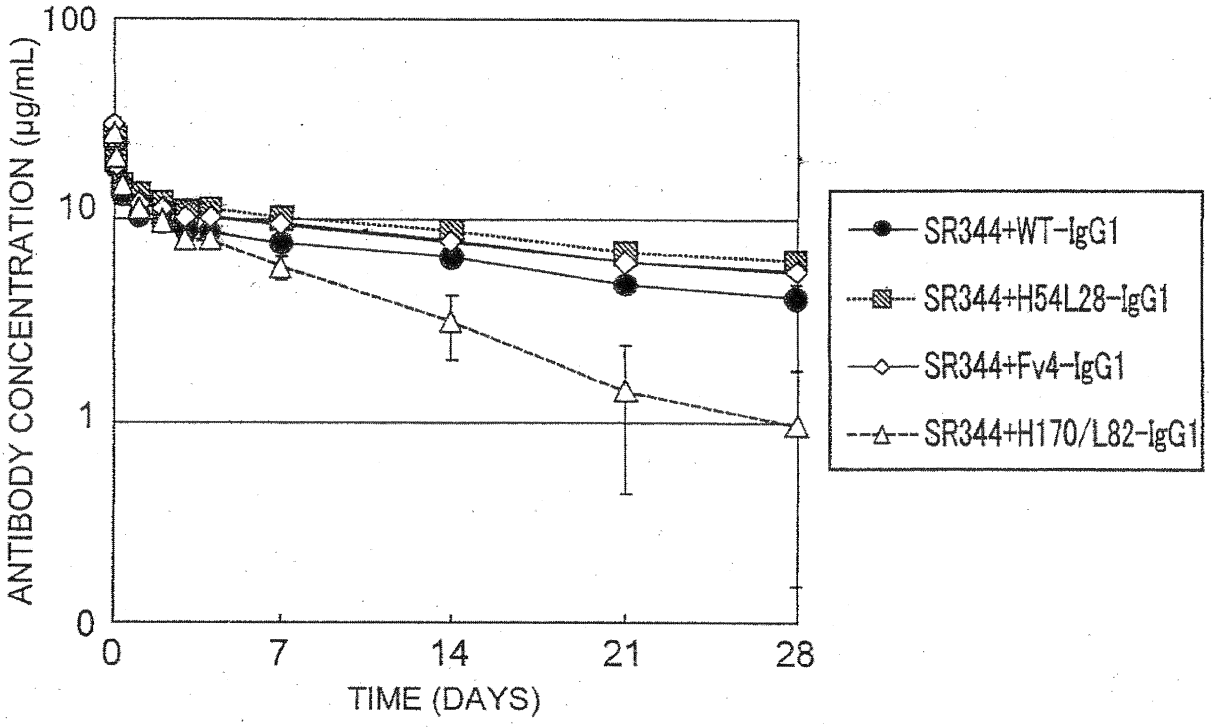

100
10
1
0
ANTIBODY CONCENTRATION (μg/mL)
0
7
14
21
28
TIME (DAYS)
SR344+WT-IgG1
SR344+H54L28-IgG1
SR344+Fv4-IgG1
SR344+H170/L82-IgG1

FIG. 28

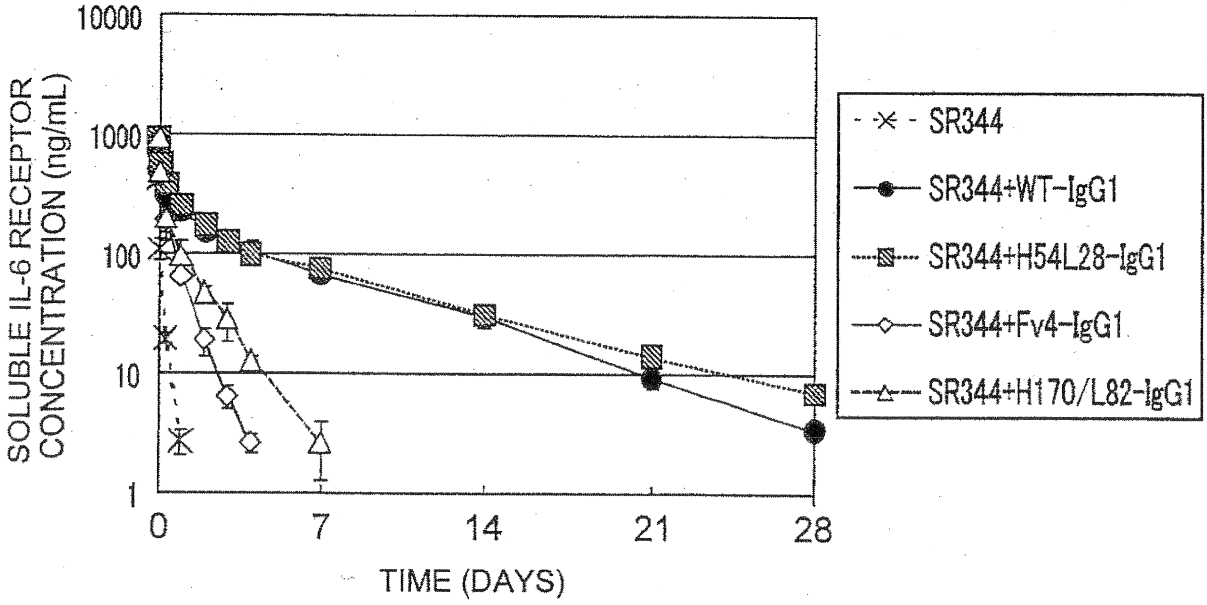

10000
1000
100
10
1
SOLUBLE IL-6 RECEPTOR CONCENTRATION (ng/mL)
0
7
14
21
28
TIME (DAYS)
SR344
SR344+WT-IgG1
SR344+H54L28-IgG1
SR344+Fv4-IgG1
SR344+H170/L82-IgG1

FIG. 29