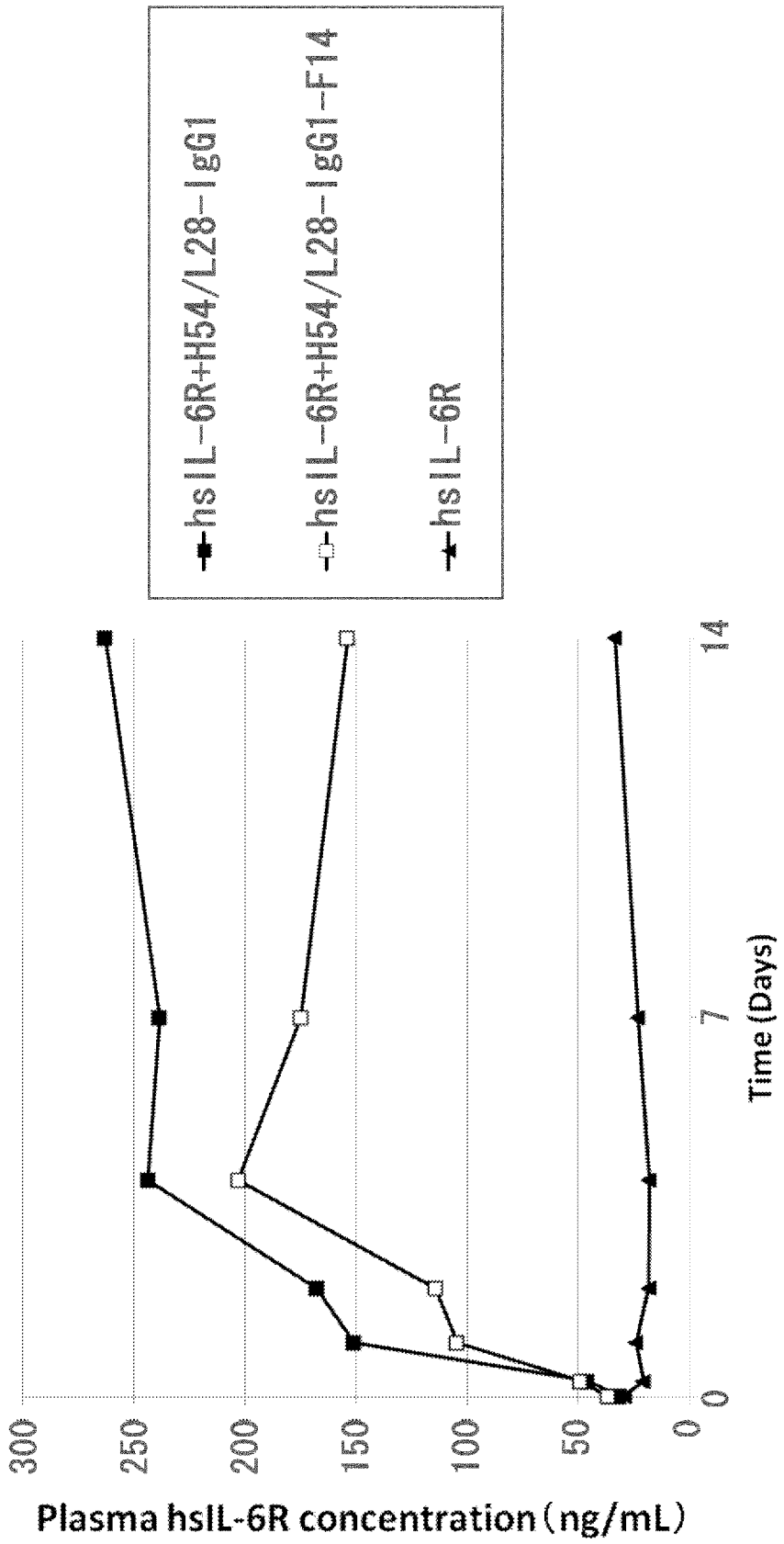
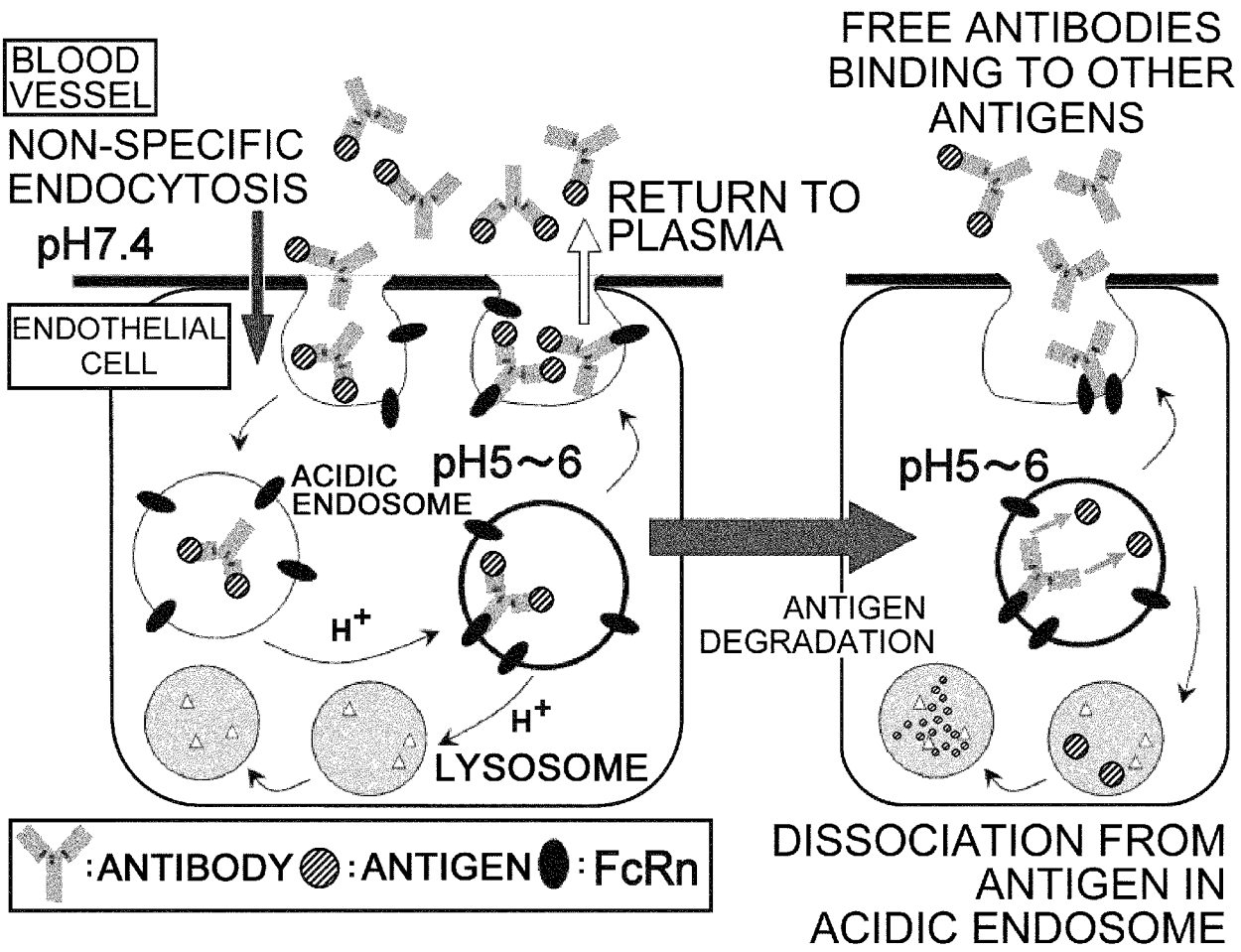
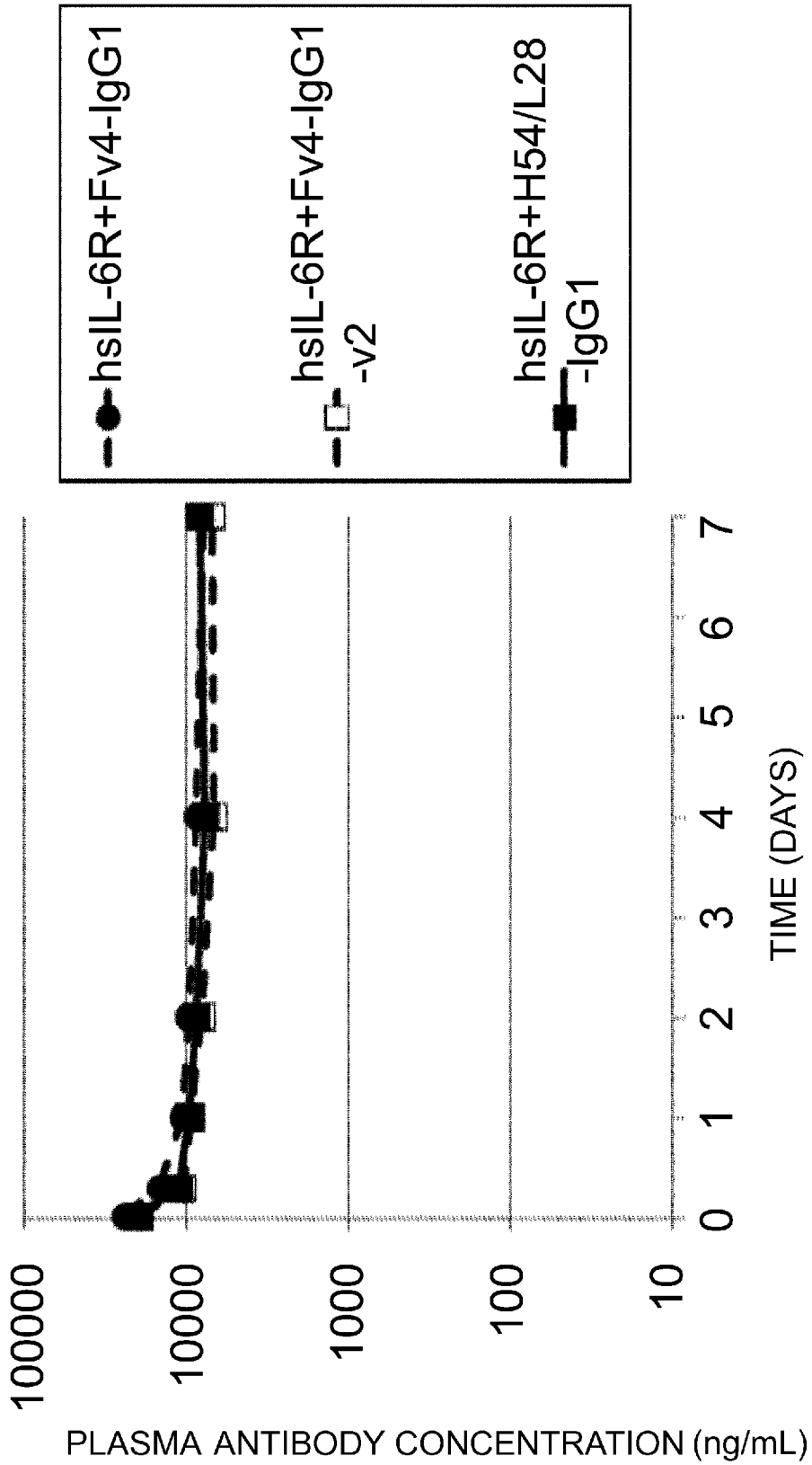
[Fig. 1]


hsIL-6R+H54/L28-IgG1
hsIL-6R+H54/L28-IgG1-F14
hsIL-6R
300
250
200
150
100
50
0
0
7
14
Time (Days)
Plasma hsIL-6R concentration (ng/mL)

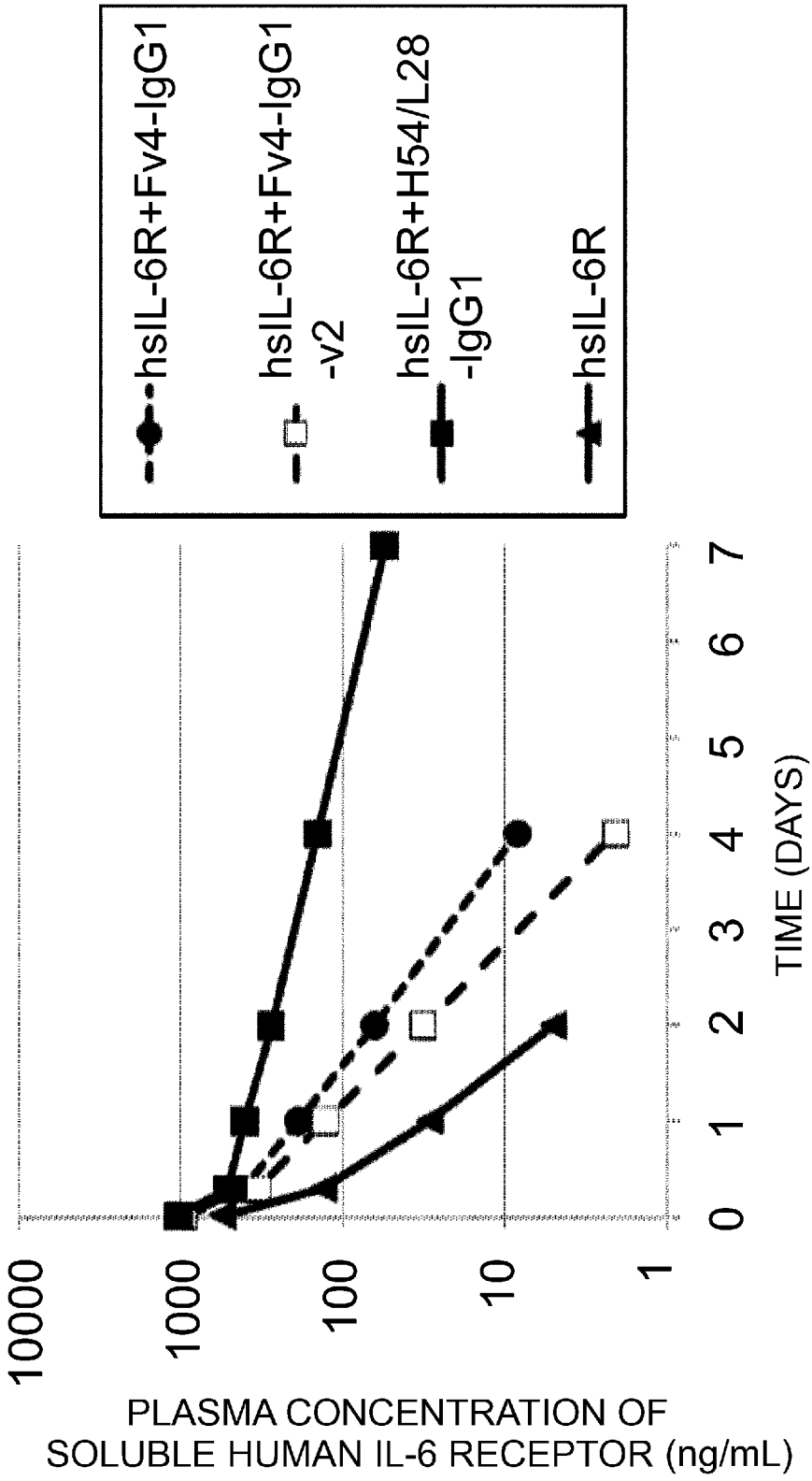
[Fig. 2]


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

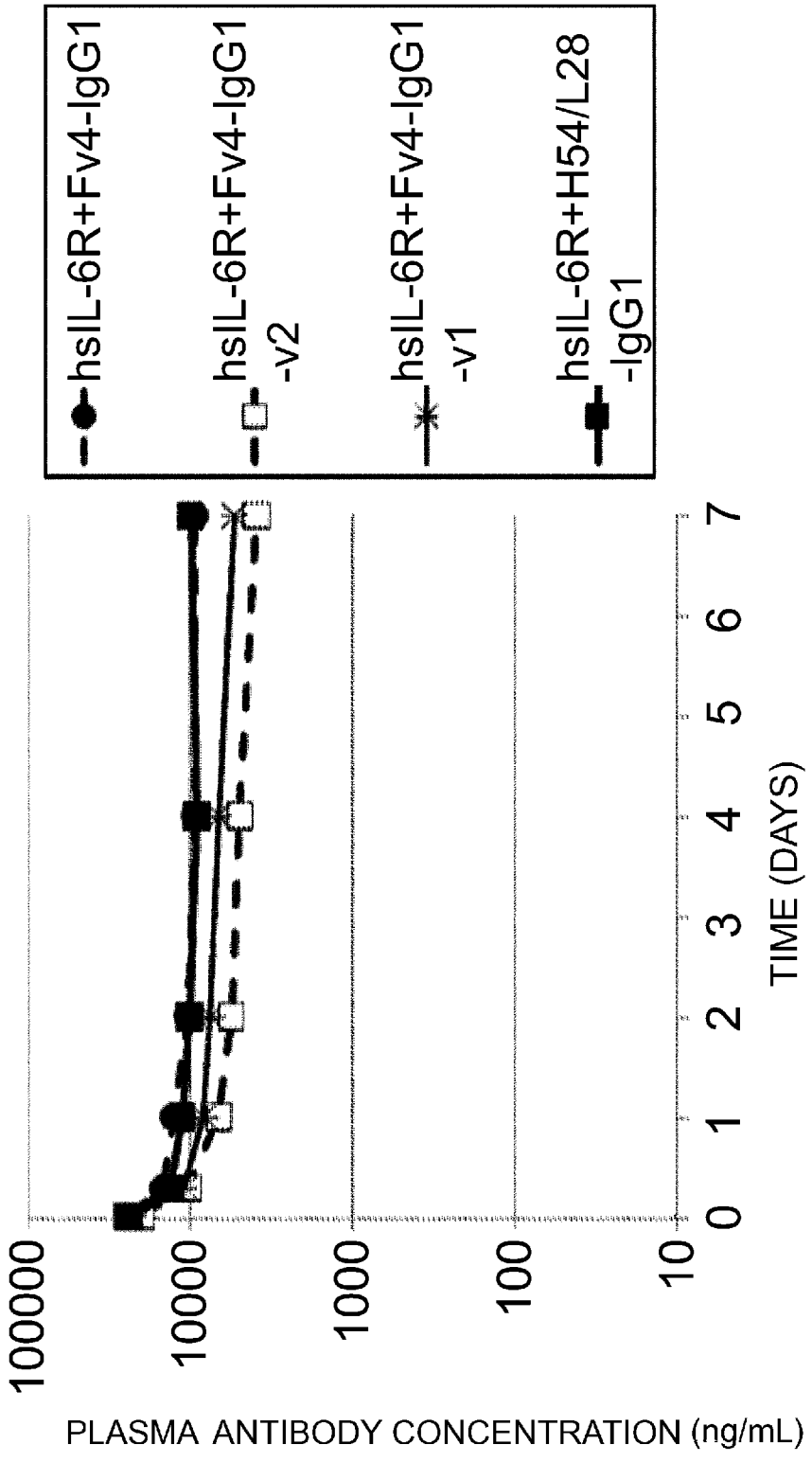
[Fig. 3]


hsIL-6R+Fv4-IgG1
hsIL-6R+Fv4-IgG1 -v2
hsIL-6R+H54/L28 -IgG1
100000
10000
1000
100
10
0 1 2 3 4 5 6 7
TIME (DAYS)
PLASMA ANTIBODY CONCENTRATION (ng/mL)

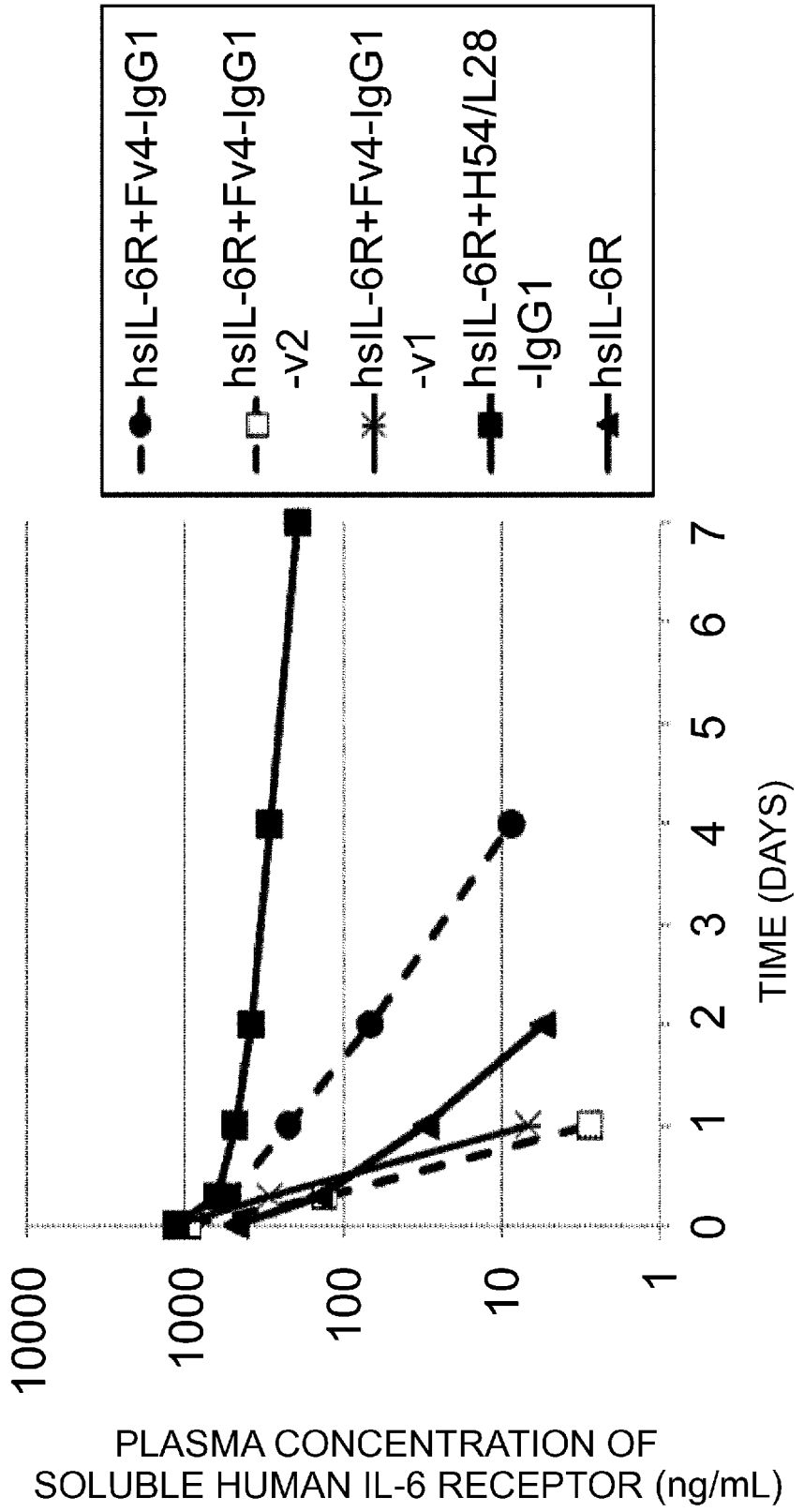
[Fig. 4]


hsIL-6R+Fv4-IgG1
hsIL-6R+Fv4-IgG1 -v2
hsIL-6R+H54/L28 -IgG1
hsIL-6R
10000
1000
100
10
1
0 1 2 3 4 5 6 7
TIME (DAYS)
PLASMA CONCENTRATION OF SOLUBLE HUMAN IL-6 RECEPTOR (ng/mL)

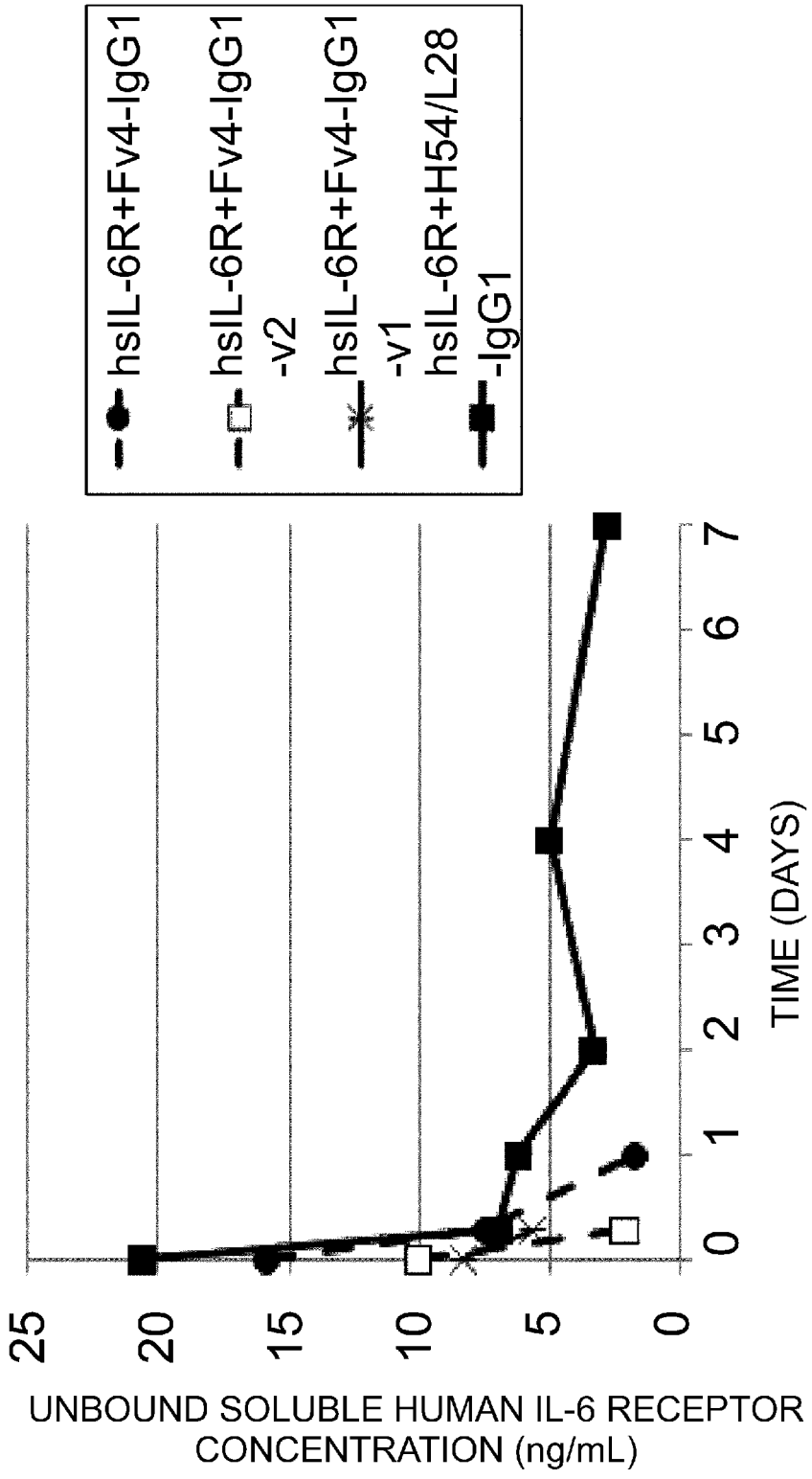
[Fig. 5]


hsIL-6R+Fv4-IgG1
hsIL-6R+Fv4-IgG1 -v2
hsIL-6R+Fv4-IgG1 -v1
hsIL-6R+H54/L28 -IgG1
100000
10000
1000
100
10
0
1
2
3
4
5
6
7
TIME (DAYS)
PLASMA ANTIBODY CONCENTRATION (ng/mL)

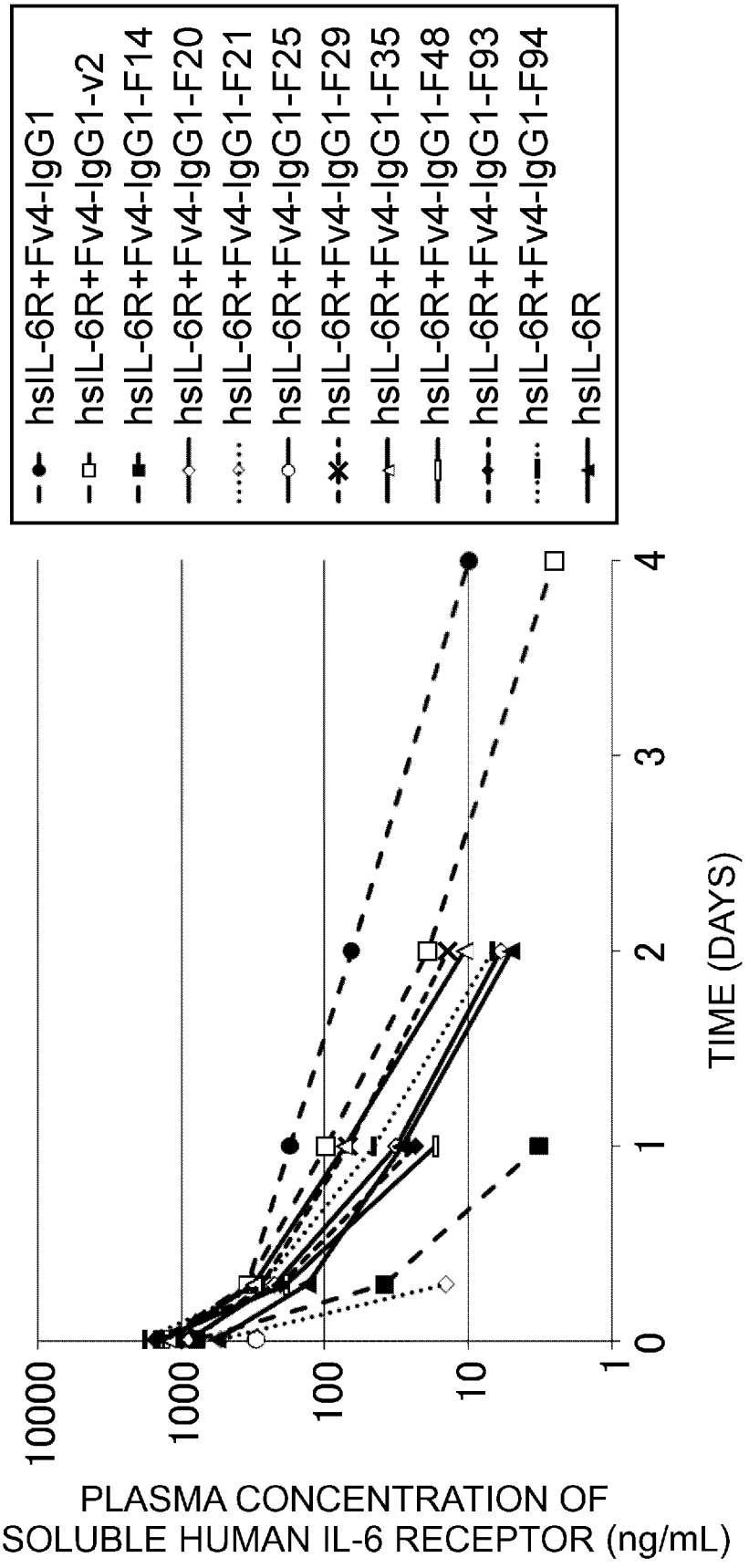
[Fig. 6]


hsIL-6R+Fv4-IgG1
hsIL-6R+Fv4-IgG1 -v2
hsIL-6R+Fv4-IgG1 -v1
hsIL-6R+H54/L28 -IgG1
hsIL-6R
10000
1000
100
10
1
0 1 2 3 4 5 6 7
TIME (DAYS)
PLASMA CONCENTRATION OF SOLUBLE HUMAN IL-6 RECEPTOR (ng/mL)

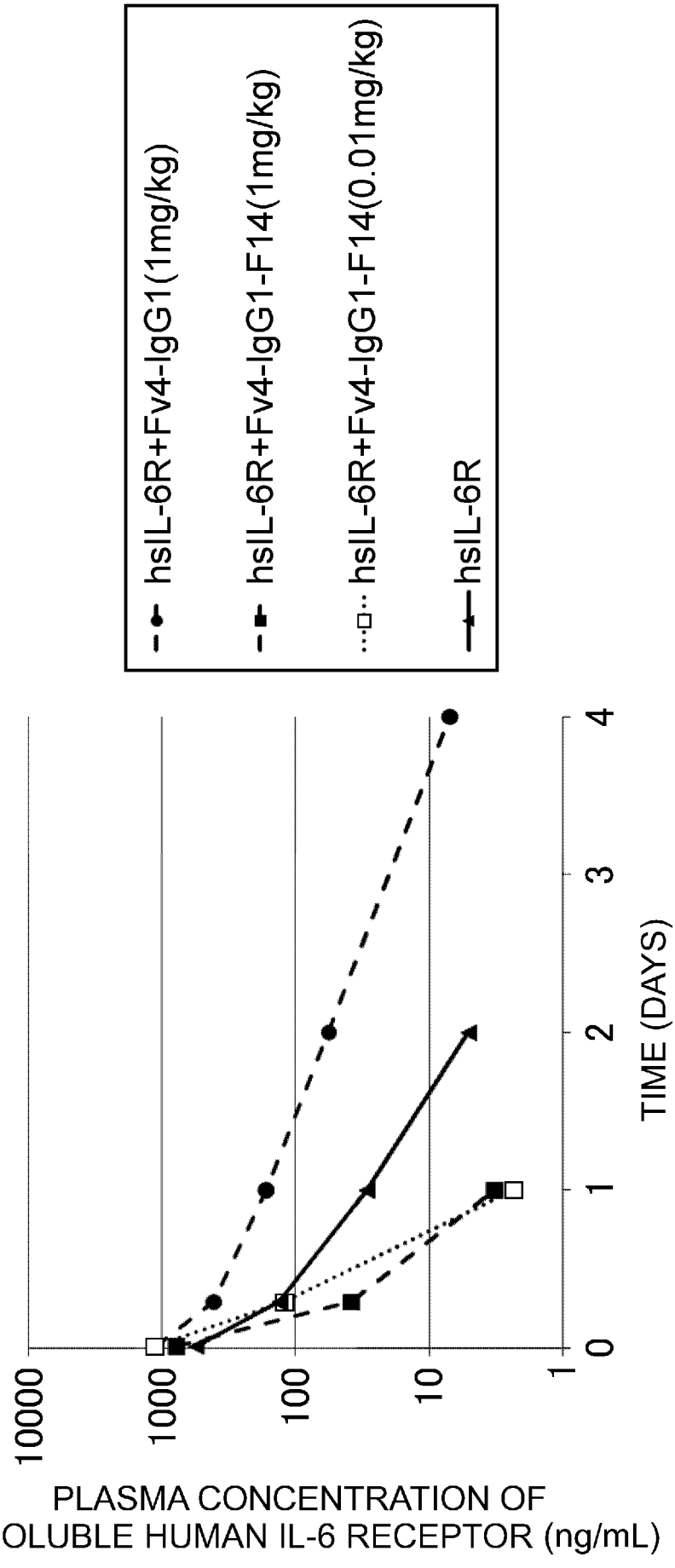
[Fig. 7]


hsIL-6R+Fv4-IgG1
hsIL-6R+Fv4-IgG1 -v2
hsIL-6R+Fv4-IgG1 -v1
hsIL-6R+H54/L28 -IgG1
25
20
15
10
5
0
0
1
2
3
4
5
6
7
TIME (DAYS)
UNBOUND SOLUBLE HUMAN IL-6 RECEPTOR CONCENTRATION (ng/mL)

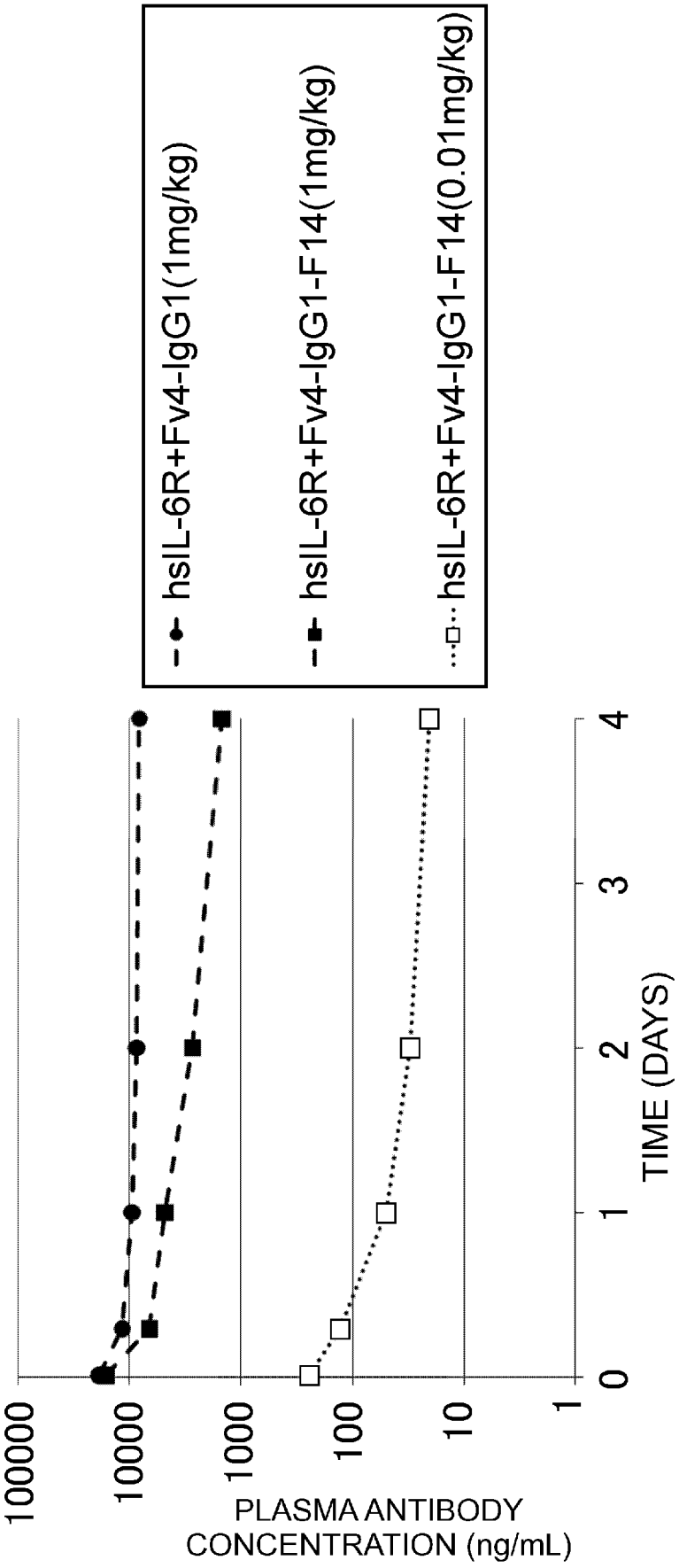
[Fig. 8]


hsIL-6R+Fv4-IgG1
hsIL-6R+Fv4-IgG1-v2
hsIL-6R+Fv4-IgG1-F14
hsIL-6R+Fv4-IgG1-F20
hsIL-6R+Fv4-IgG1-F21
hsIL-6R+Fv4-IgG1-F25
hsIL-6R+Fv4-IgG1-F29
hsIL-6R+Fv4-IgG1-F35
hsIL-6R+Fv4-IgG1-F48
hsIL-6R+Fv4-IgG1-F93
hsIL-6R+Fv4-IgG1-F94
hsIL-6R
10000
1000
100
10
1
0
1
2
3
4
TIME (DAYS)
PLASMA CONCENTRATION OF SOLUBLE HUMAN IL-6 RECEPTOR (ng/mL)

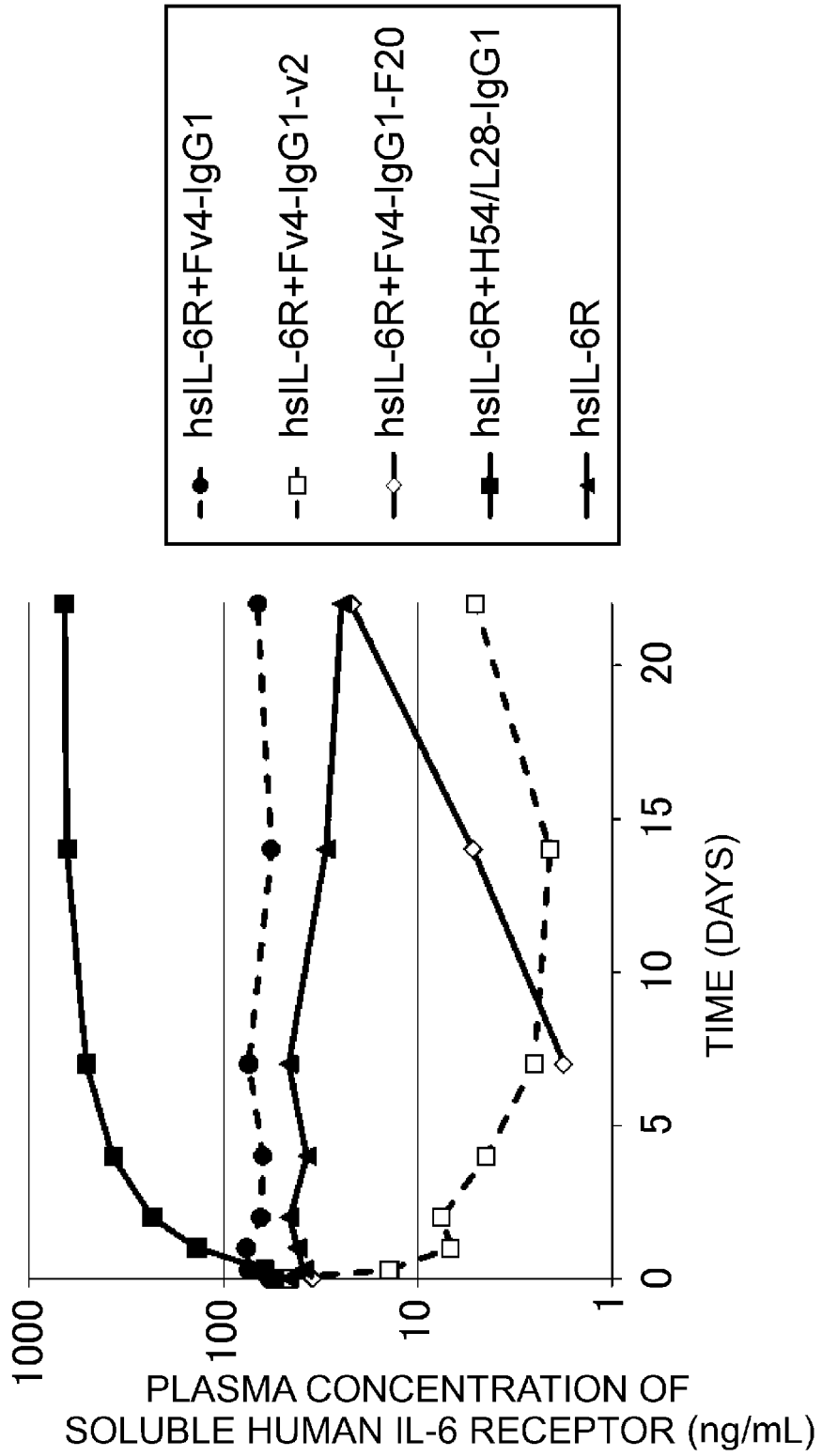
[Fig. 9]


hsIL-6R+Fv4-IgG1(1mg/kg)
hsIL-6R+Fv4-IgG1-F14(1mg/kg)
hsIL-6R+Fv4-IgG1-F14(0.01mg/kg)
hsIL-6R
10000
1000
100
10
1
0
1
2
3
4
TIME (DAYS)
PLASMA CONCENTRATION OF
SOLUBLE HUMAN IL-6 RECEPTOR (ng/mL)

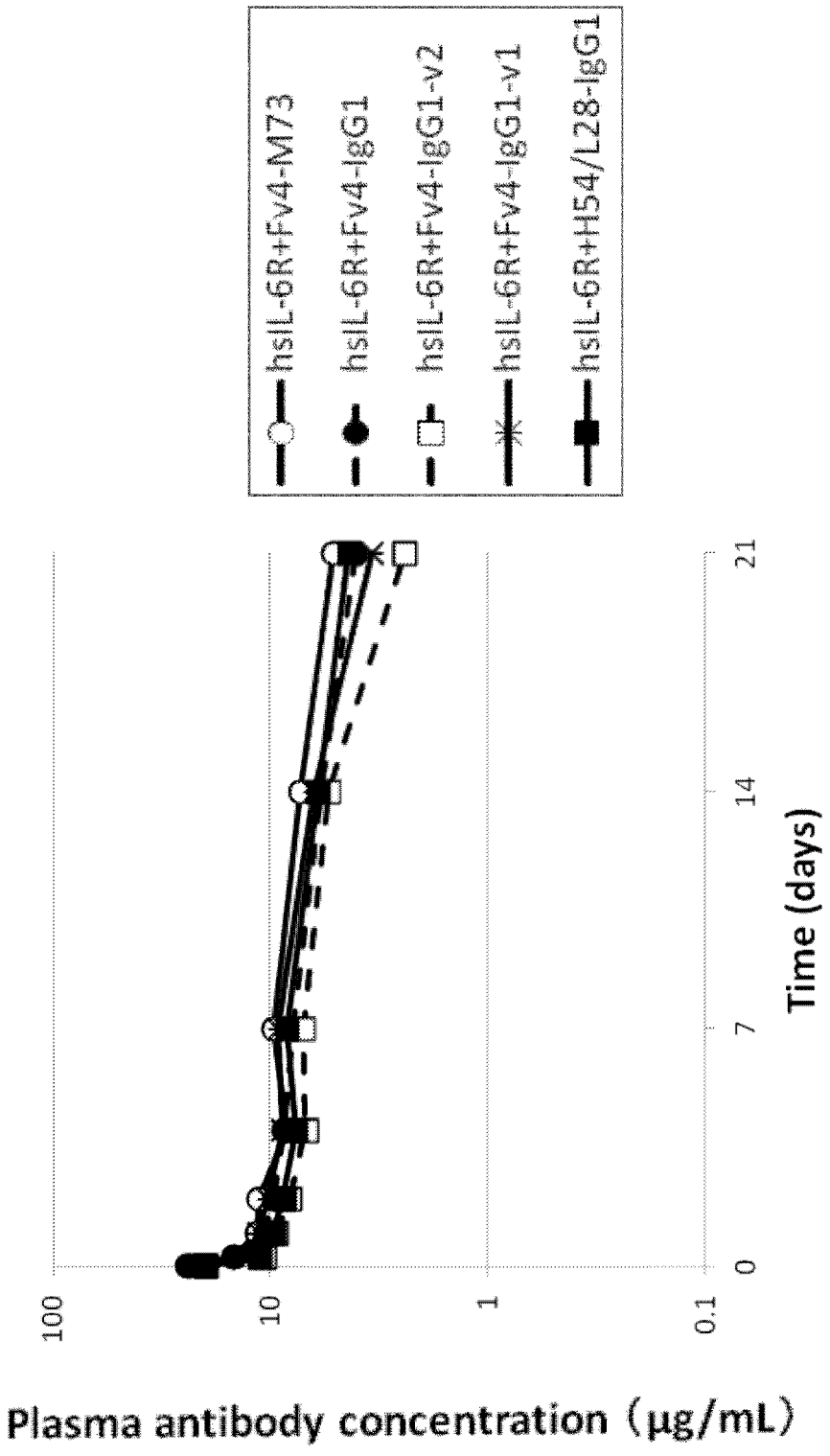
[Fig. 10]


hsIL-6R+Fv4-IgG1(1mg/kg)
hsIL-6R+Fv4-IgG1-F14(1mg/kg)
hsIL-6R+Fv4-IgG1-F14(0.01mg/kg)
100000
10000
1000
100
10
1
PLASMA ANTIBODY CONCENTRATION (ng/mL)
0
1
2
3
4
TIME (DAYS)

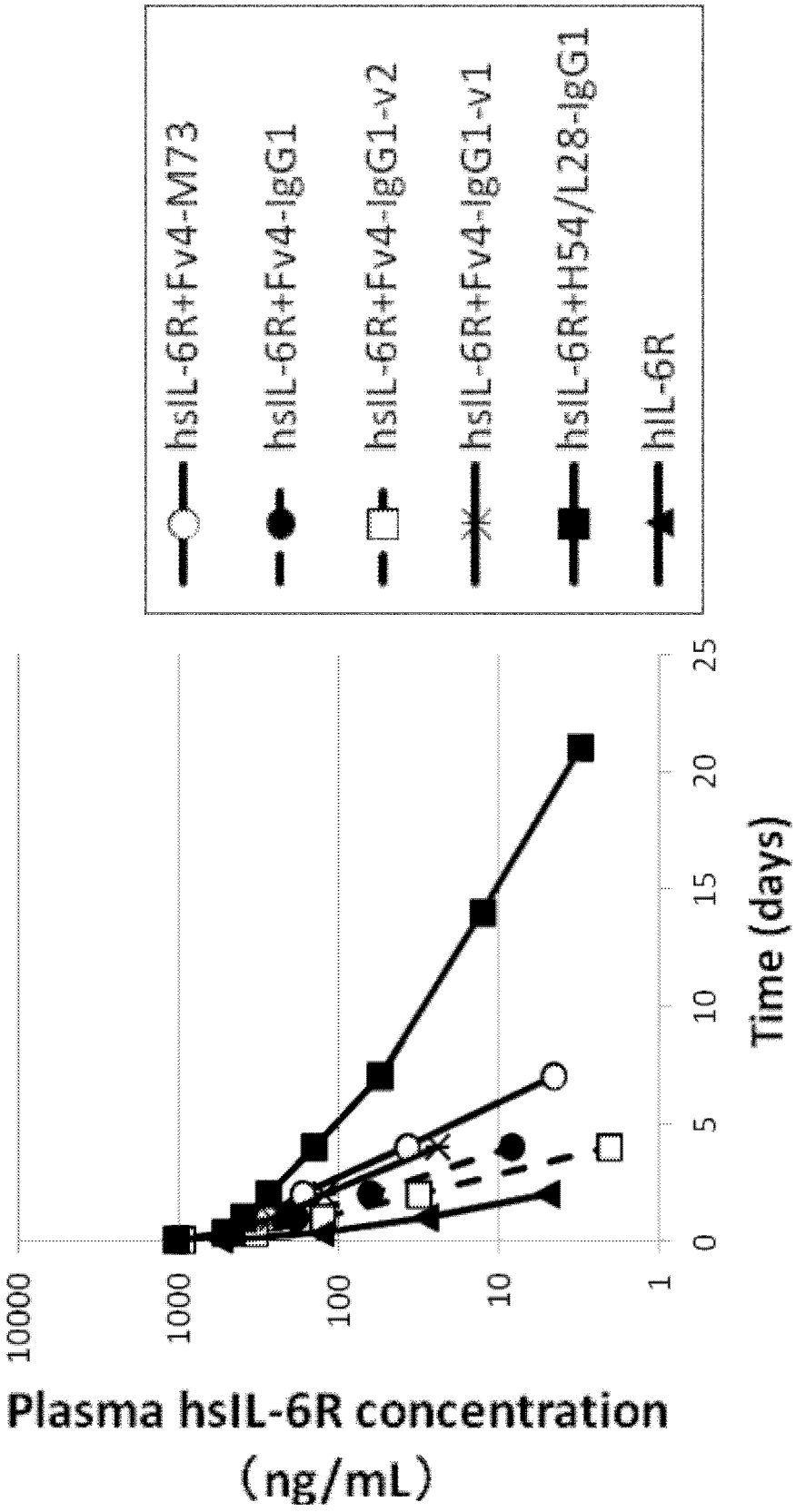
[Fig. 11]


hsIL-6R+Fv4-IgG1
hsIL-6R+Fv4-IgG1-v2
hsIL-6R+Fv4-IgG1-F20
hsIL-6R+H54/L28-IgG1
hsIL-6R
1000
100
10
1
0
5
10
15
20
TIME (DAYS)
PLASMA CONCENTRATION OF
SOLUBLE HUMAN IL-6 RECEPTOR (ng/mL)

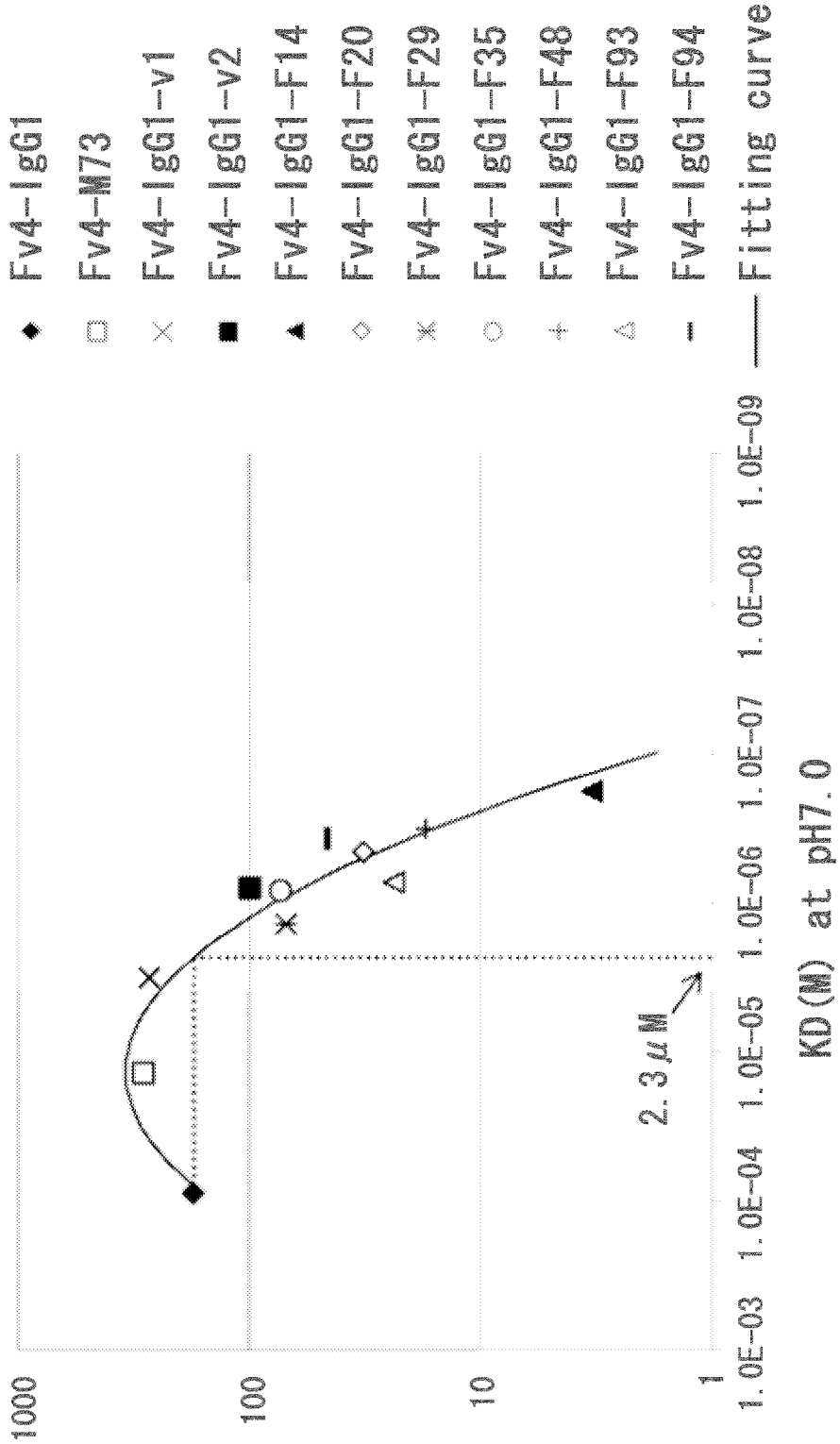
[Fig. 12]


hsIL-6R+Fv4-M73
hsIL-6R+Fv4-IgG1
hsIL-6R+Fv4-IgG1-v2
hsIL-6R+Fv4-IgG1-v1
hsIL-6R+H54/L28-IgG1
100
10
1
0.1
0
7
14
21
Time (days)
Plasma antibody concentration (μg/mL)

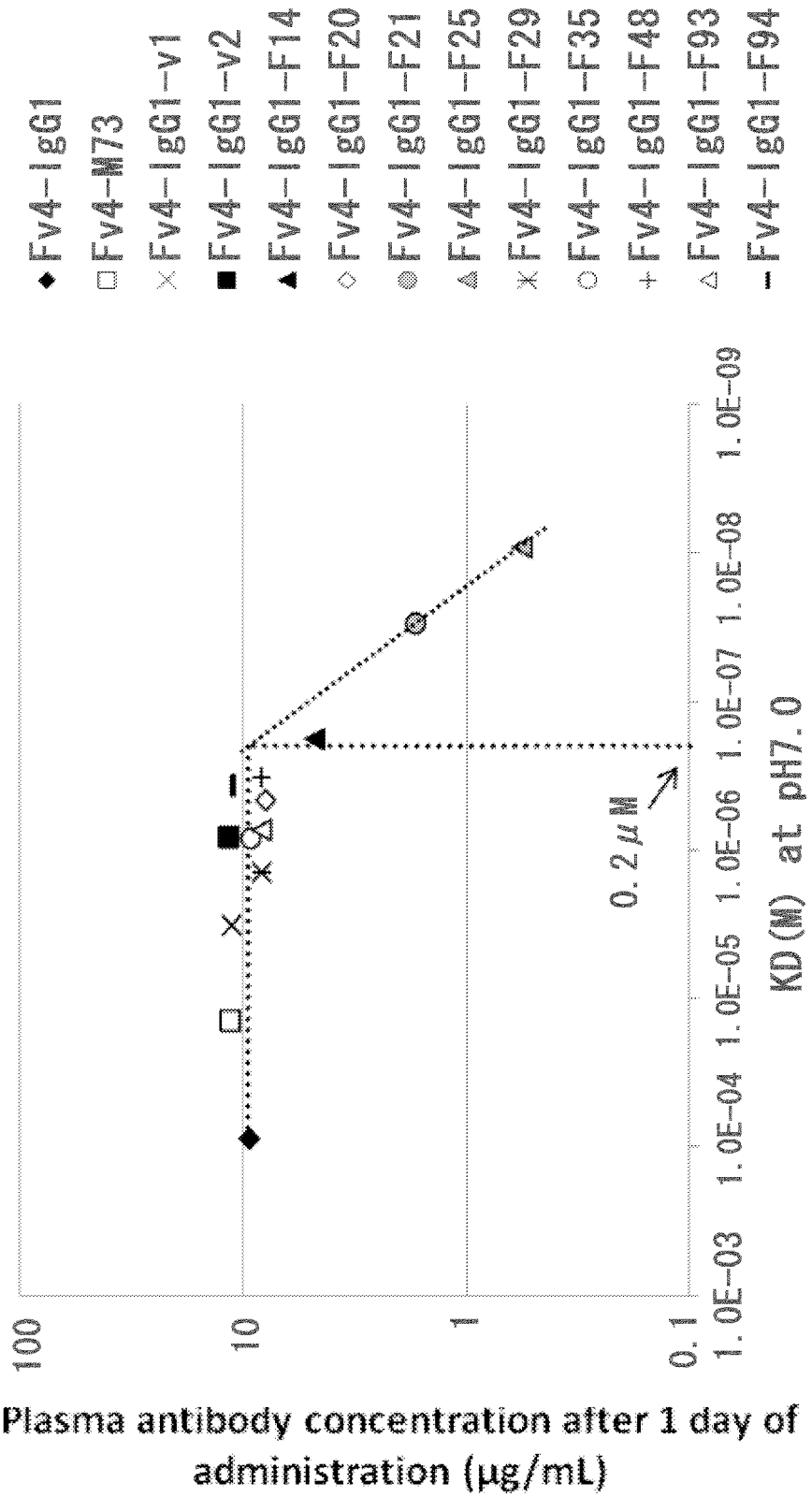
[Fig. 13]


hsIL-6R+Fv4-M73
hsIL-6R+Fv4-IgG1
hsIL-6R+Fv4-IgG1-v2
hsIL-6R+Fv4-IgG1-v1
hsIL-6R+H54/L28-IgG1
hIL-6R
10000
1000
100
10
1
0
5
10
15
20
25
Time (days)
Plasma hsIL-6R concentration
(ng/mL)

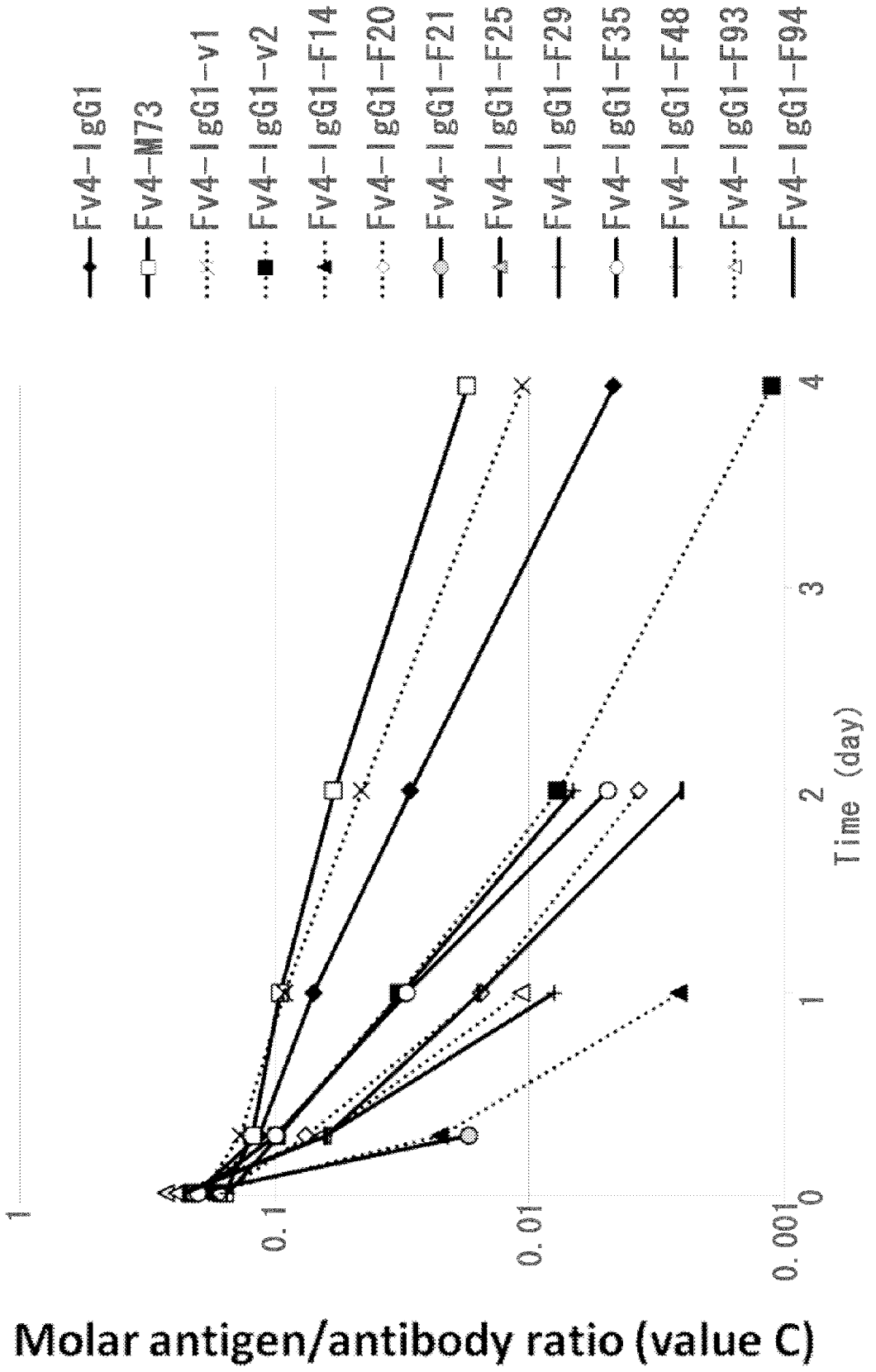
[Fig. 14]


Fv4-IgG1
Fv4-M73
Fv4-IgG1-v1
Fv4-IgG1-v2
Fv4-IgG1-F14
Fv4-IgG1-F20
Fv4-IgG1-F29
Fv4-IgG1-F35
Fv4-IgG1-F48
Fv4-IgG1-F93
Fv4-IgG1-F94
Fitting curve
1000
100
10
1
1.0E-03
1.0E-04
1.0E-05
1.0E-06
1.0E-07
1.0E-08
1.0E-09
KD(M) at pH7.0
2.3μM
Plasma hsIL-6R concentration after 1 day of administration (ng/mL)

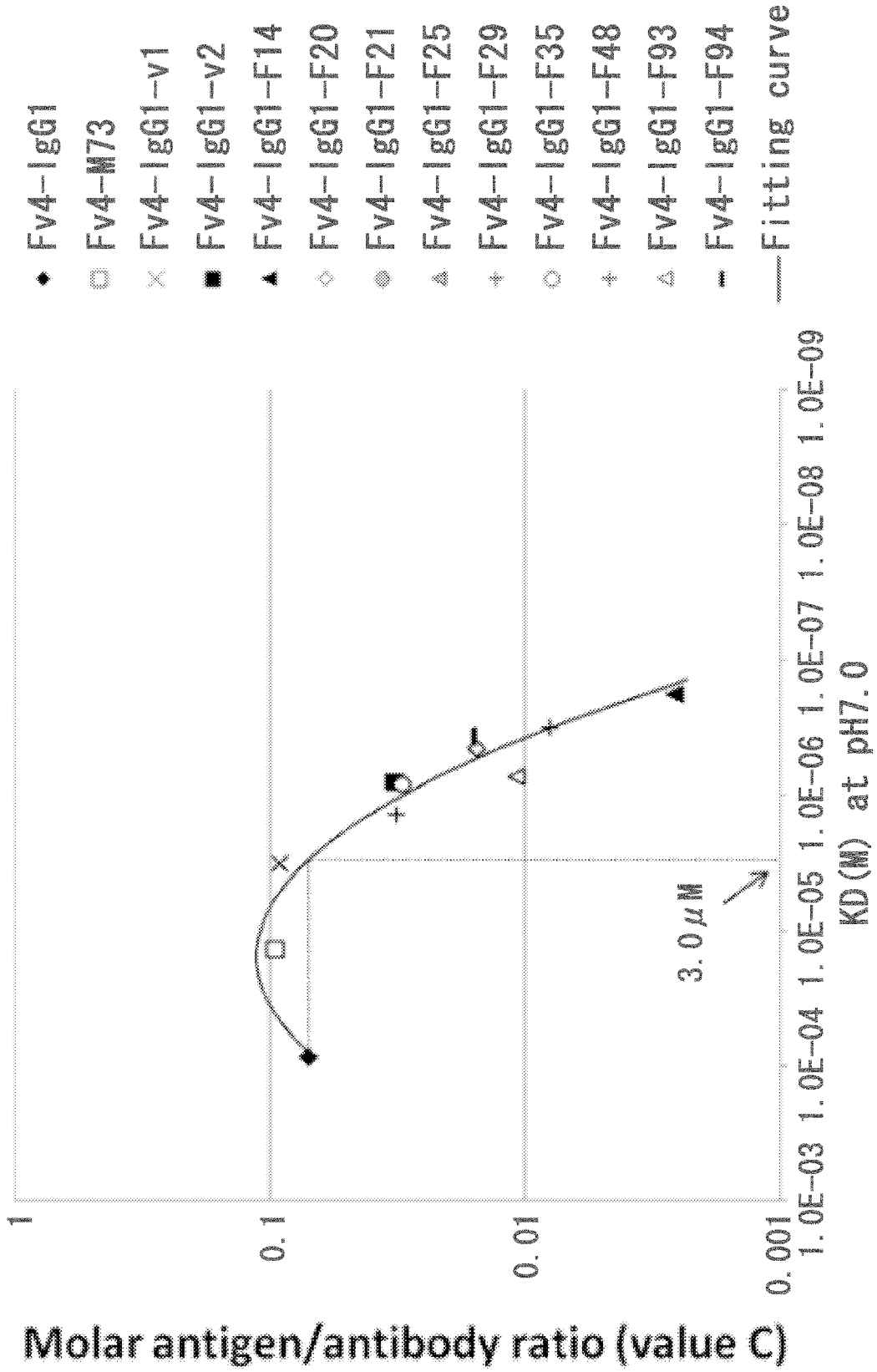
[Fig. 15]


Fv4-IgG1
Fv4-M73
Fv4-IgG1-v1
Fv4-IgG1-v2
Fv4-IgG1-F14
Fv4-IgG1-F20
Fv4-IgG1-F21
Fv4-IgG1-F25
Fv4-IgG1-F29
Fv4-IgG1-F35
Fv4-IgG1-F48
Fv4-IgG1-F93
Fv4-IgG1-F94
100
10
1
0.1
1.0E-03
1.0E-04
1.0E-05
1.0E-06
1.0E-07
1.0E-08
1.0E-09
KD(M) at pH7.0
0.2μM
Plasma antibody concentration after 1 day of administration (μg/mL)

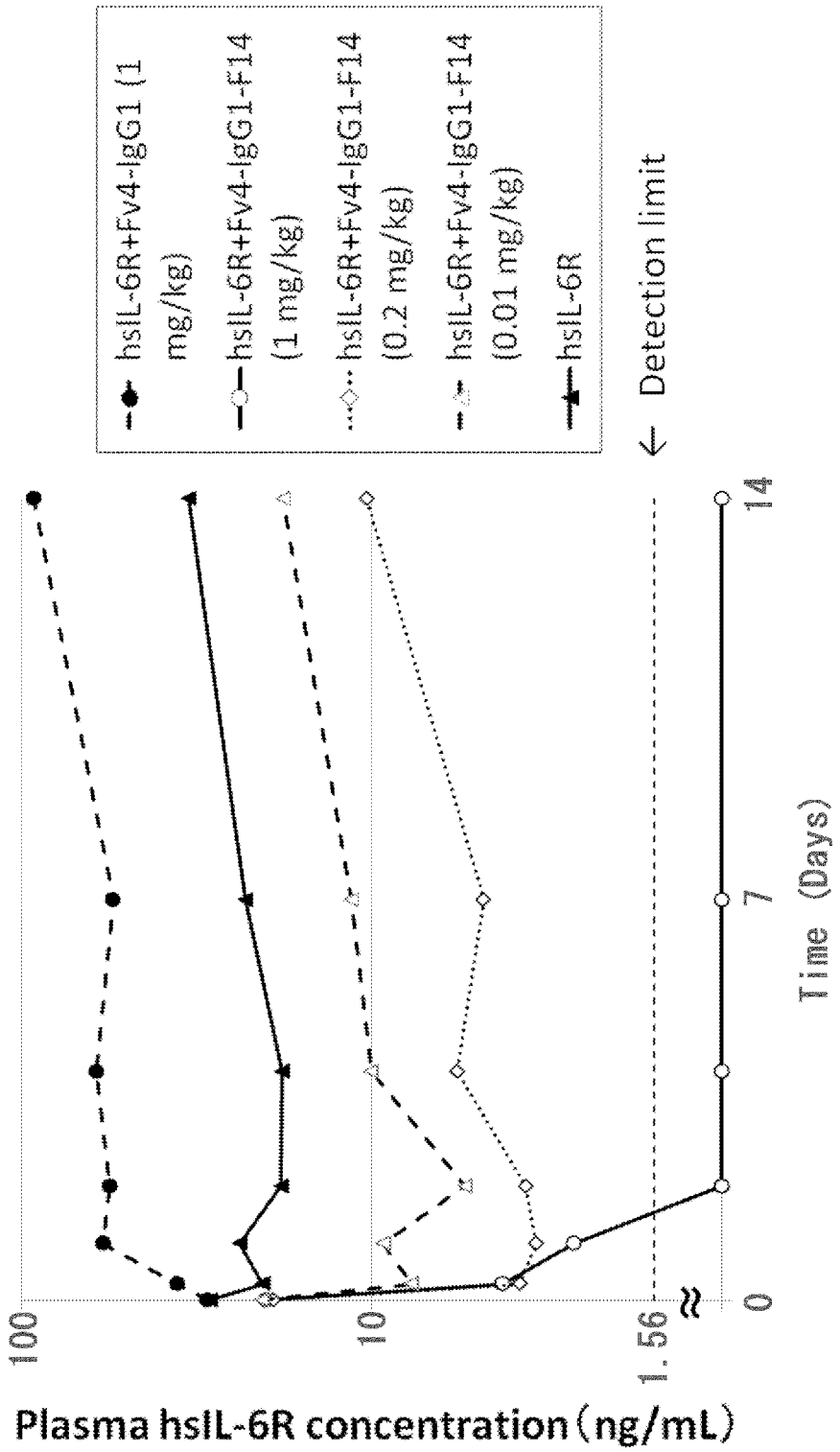
[Fig. 16]


Fv4-IgG1
Fv4-M73
Fv4-IgG1-v1
Fv4-IgG1-v2
Fv4-IgG1-F14
Fv4-IgG1-F20
Fv4-IgG1-F21
Fv4-IgG1-F25
Fv4-IgG1-F29
Fv4-IgG1-F35
Fv4-IgG1-F48
Fv4-IgG1-F93
Fv4-IgG1-F94
1
0.1
0.01
0.001
0
1
2
3
4
Time (day)
Molar antigen/antibody ratio (value C)

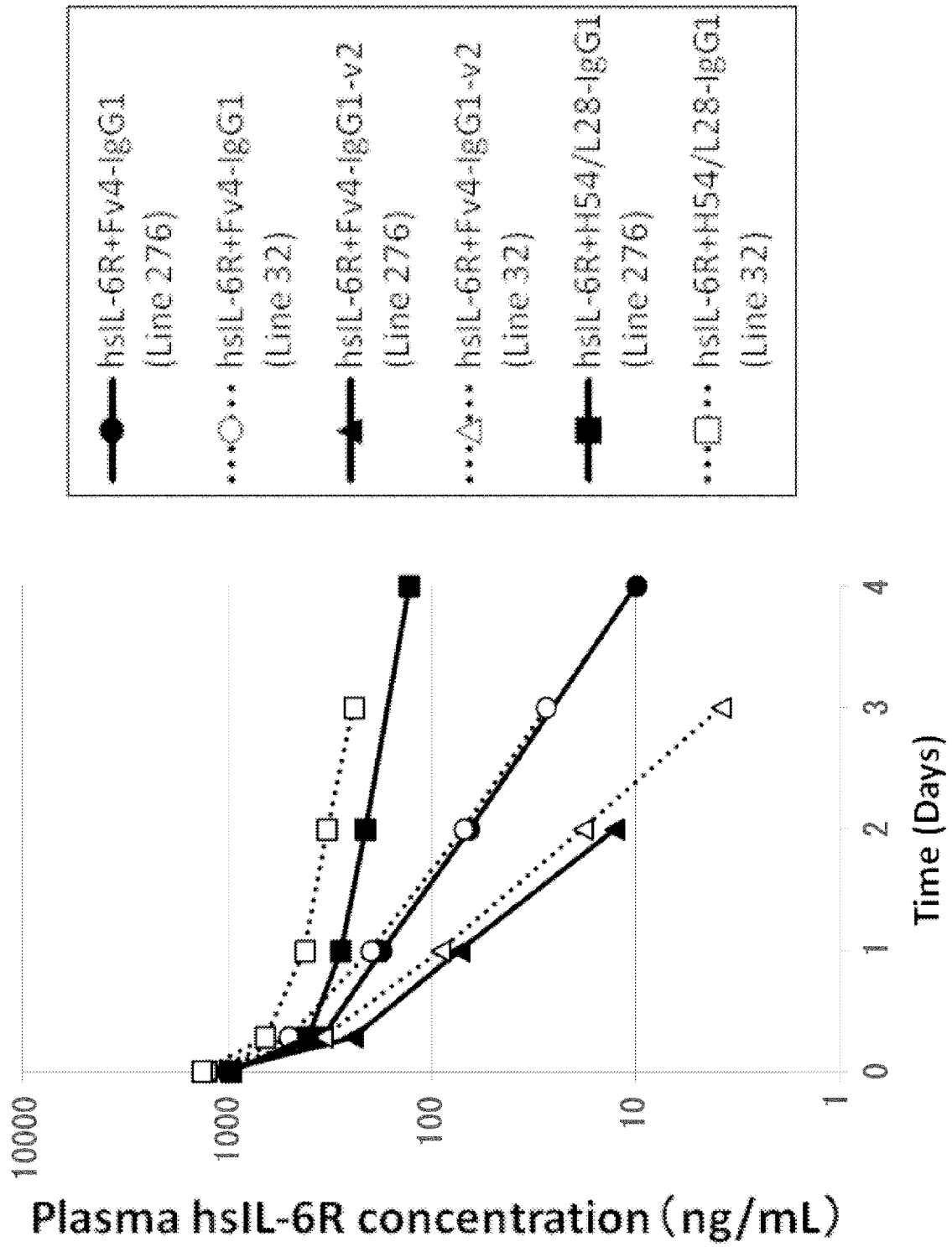
[Fig. 17]


Fv4-IgG1
Fv4-M73
Fv4-IgG1-v1
Fv4-IgG1-v2
Fv4-IgG1-F14
Fv4-IgG1-F20
Fv4-IgG1-F21
Fv4-IgG1-F25
Fv4-IgG1-F29
Fv4-IgG1-F35
Fv4-IgG1-F48
Fv4-IgG1-F93
Fv4-IgG1-F94
Fitting curve
1
0.1
0.01
0.001
1.0E-03
1.0E-04
1.0E-05
1.0E-06
1.0E-07
1.0E-08
1.0E-09
KD(M) at pH7.0
3.0μM
Molar antigen/antibody ratio (value C)

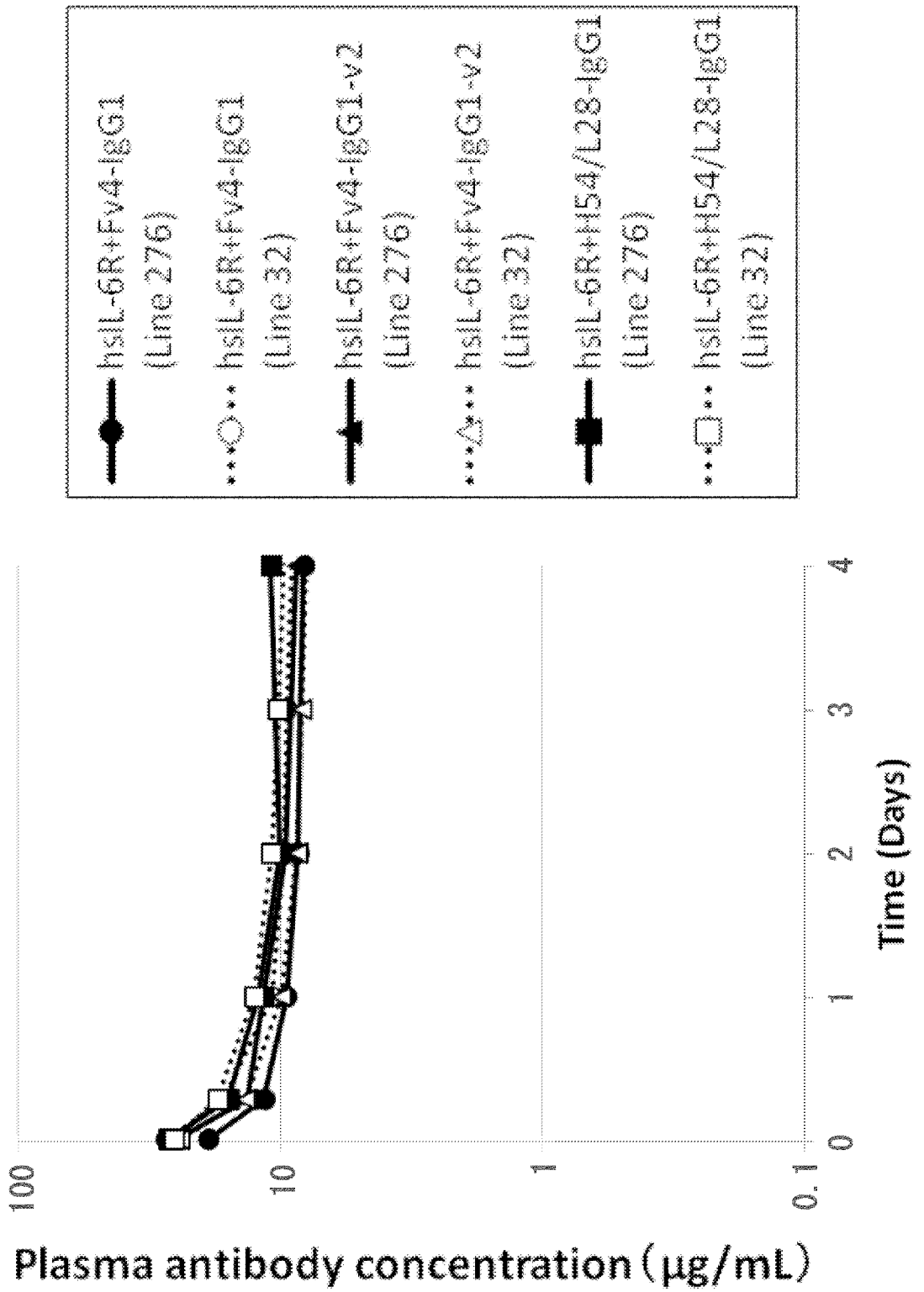
[Fig. 18]


hsIL-6R+Fv4-IgG1 (1 mg/kg)
hsIL-6R+Fv4-IgG1-F14 (1 mg/kg)
hsIL-6R+Fv4-IgG1-F14 (0.2 mg/kg)
hsIL-6R+Fv4-IgG1-F14 (0.01 mg/kg)
hsIL-6R
Detection limit
100
10
1.56
0
7
14
Time (Days)
Plasma hsIL-6R concentration (ng/mL)

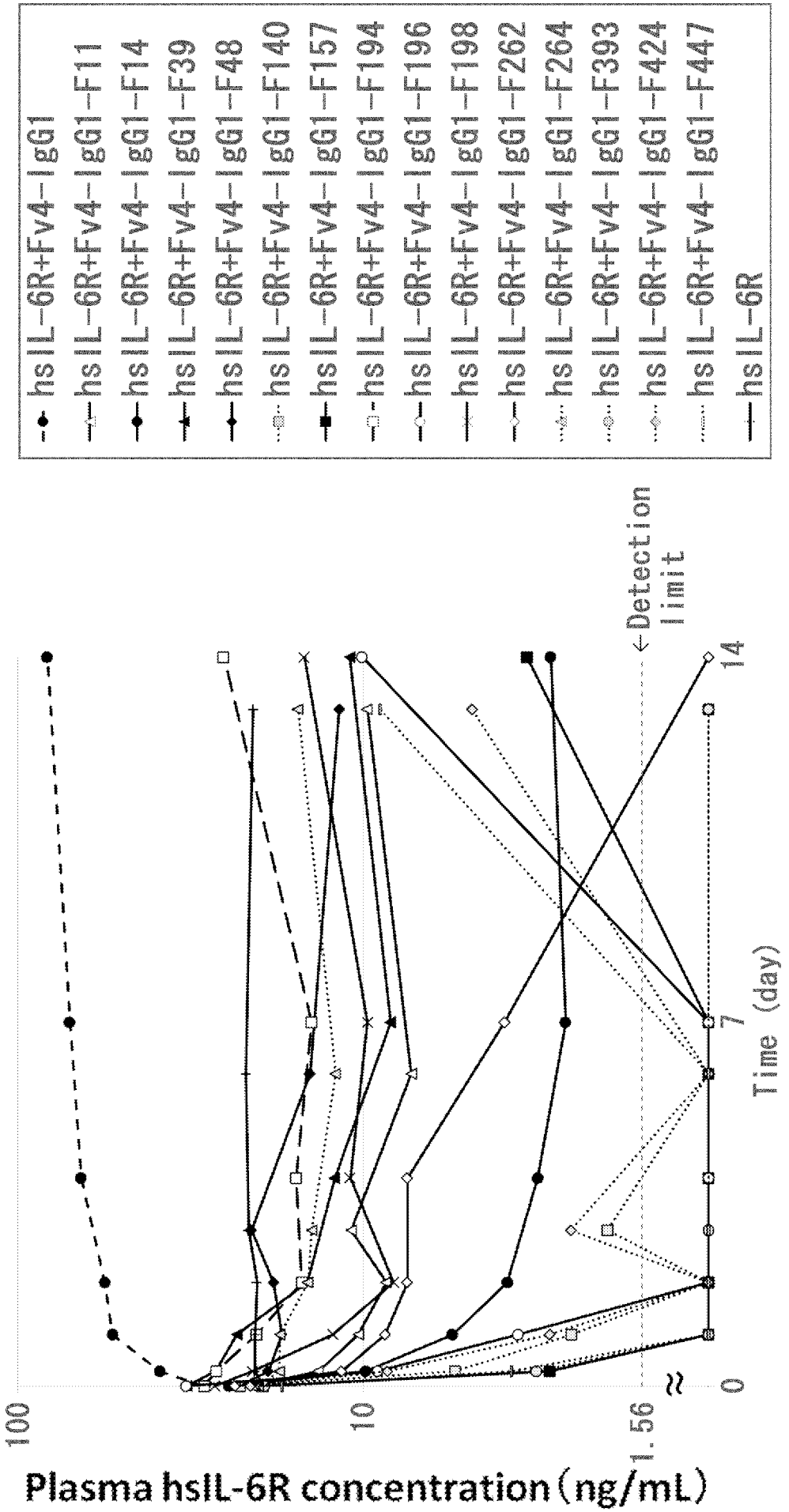
[Fig. 19]


hsIL-6R+Fv4-IgG1 (Line 276)
hsIL-6R+Fv4-IgG1 (Line 32)
hsIL-6R+Fv4-IgG1-v2 (Line 276)
hsIL-6R+Fv4-IgG1-v2 (Line 32)
hsIL-6R+H54/L28-IgG1 (Line 276)
hsIL-6R+H54/L28-IgG1 (Line 32)
10000
1000
100
10
1
0
1
2
3
4
Time (Days)
Plasma hsIL-6R concentration (ng/mL)

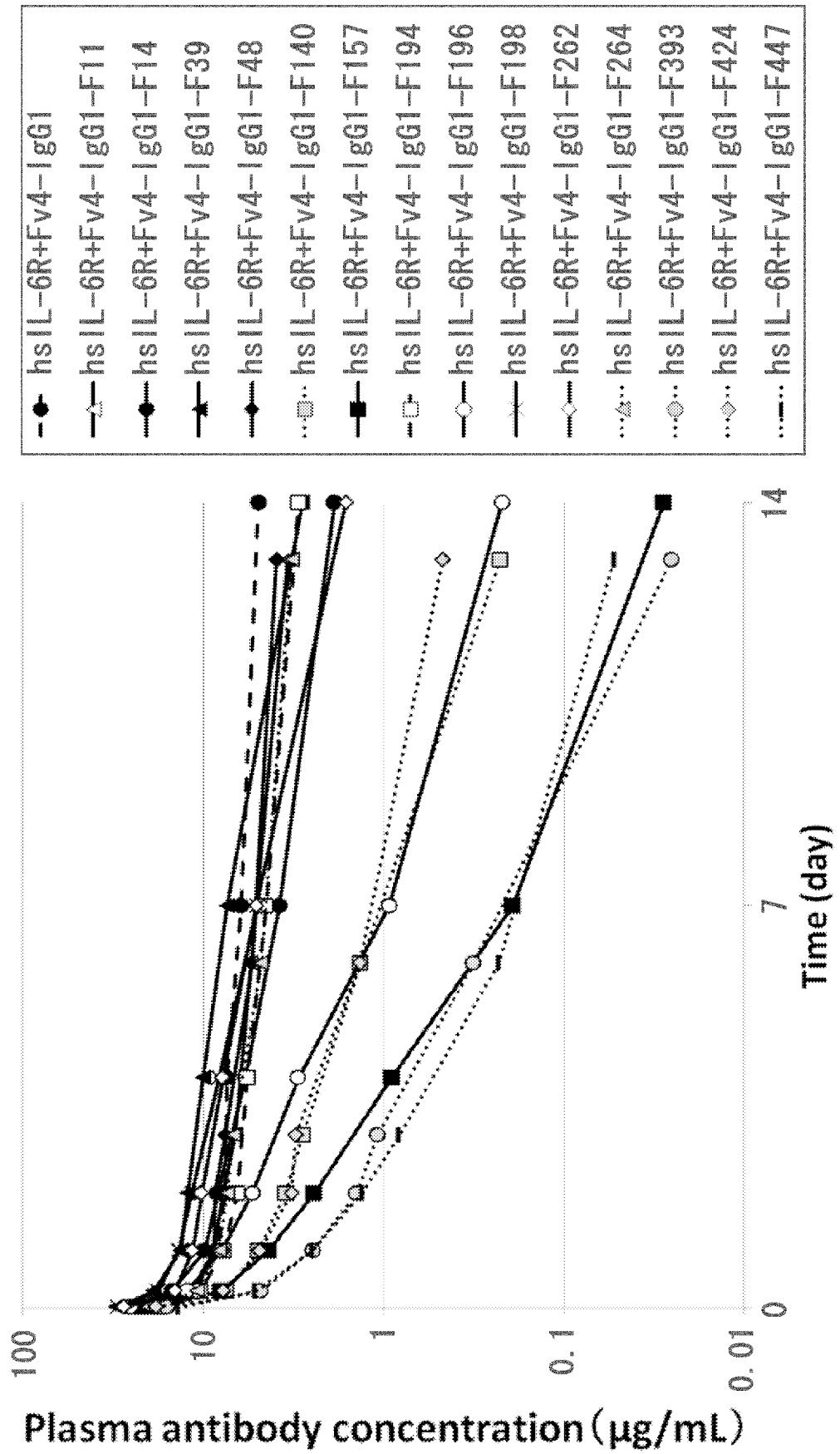
[Fig. 20]


hsIL-6R+Fv4-IgG1 (Line 276)
hsIL-6R+Fv4-IgG1 (Line 32)
hsIL-6R+Fv4-IgG1-v2 (Line 276)
hsIL-6R+Fv4-IgG1-v2 (Line 32)
hsIL-6R+H54/L28-IgG1 (Line 276)
hsIL-6R+H54/L28-IgG1 (Line 32)
100
10
1
0.1
0
1
2
3
4
Time (Days)
Plasma antibody concentration (μg/mL)

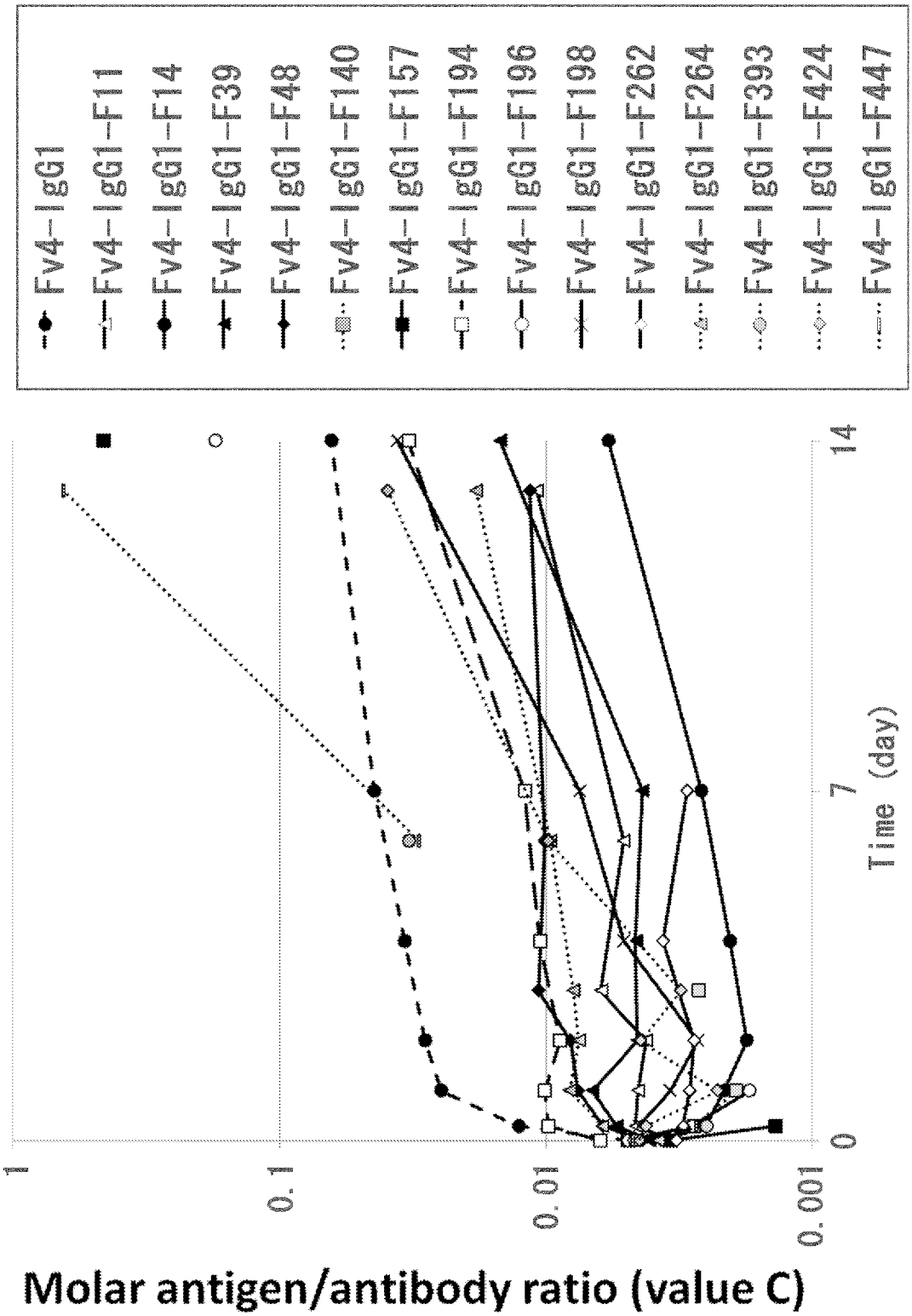
[Fig. 21]


hsIL-6R+Fv4-IgG1
hsIL-6R+Fv4-IgG1-F11
hsIL-6R+Fv4-IgG1-F14
hsIL-6R+Fv4-IgG1-F39
hsIL-6R+Fv4-IgG1-F48
hsIL-6R+Fv4-IgG1-F140
hsIL-6R+Fv4-IgG1-F157
hsIL-6R+Fv4-IgG1-F194
hsIL-6R+Fv4-IgG1-F196
hsIL-6R+Fv4-IgG1-F198
hsIL-6R+Fv4-IgG1-F262
hsIL-6R+Fv4-IgG1-F264
hsIL-6R+Fv4-IgG1-F393
hsIL-6R+Fv4-IgG1-F424
hsIL-6R+Fv4-IgG1-F447
hsIL-6R
Detection limit
100
10
1.56
0
7
14
Time (day)
Plasma hsIL-6R concentration (ng/mL)

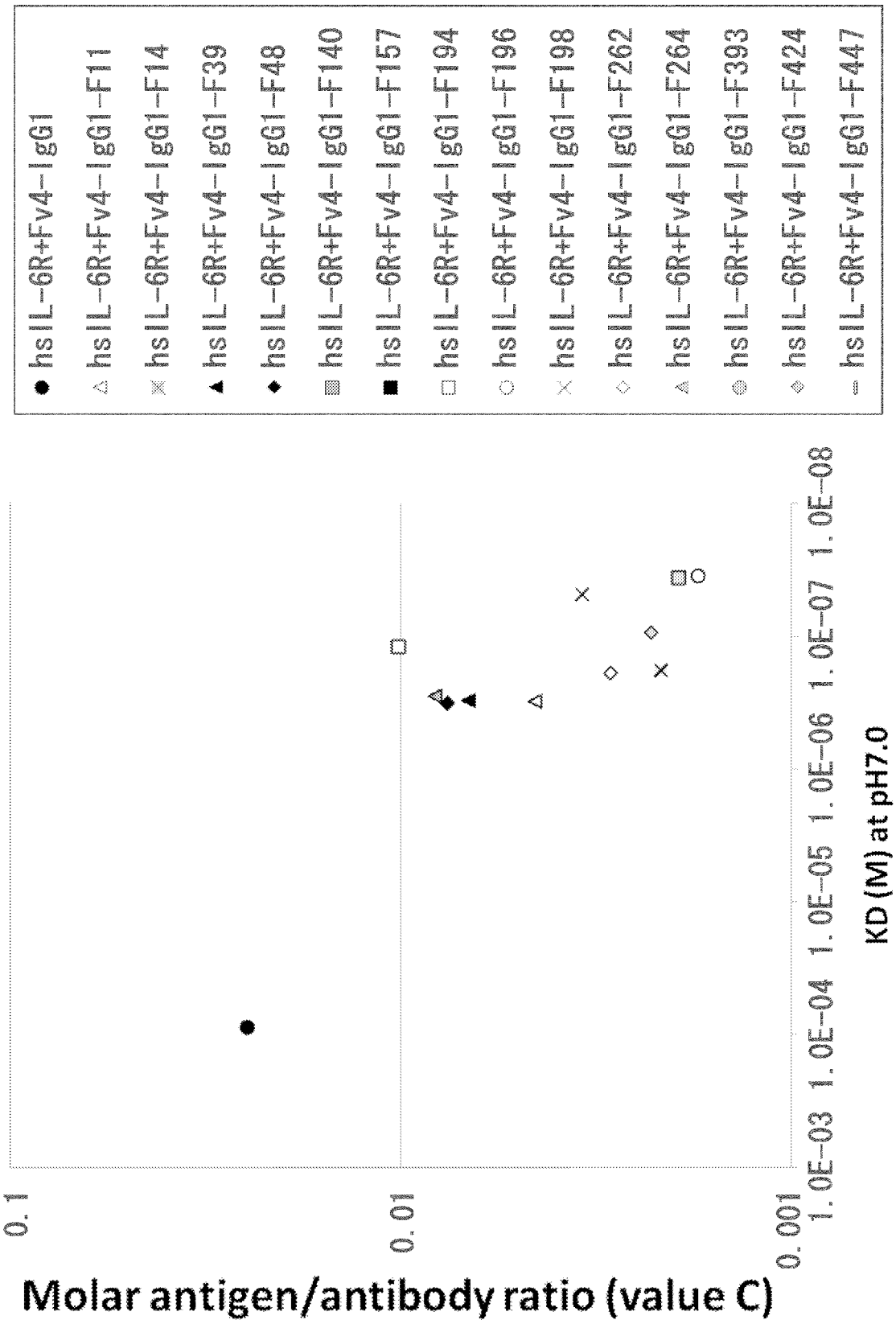
[Fig. 22]


hsIL-6R+Fv4-IgG1
hsIL-6R+Fv4-IgG1-F11
hsIL-6R+Fv4-IgG1-F14
hsIL-6R+Fv4-IgG1-F39
hsIL-6R+Fv4-IgG1-F48
hsIL-6R+Fv4-IgG1-F140
hsIL-6R+Fv4-IgG1-F157
hsIL-6R+Fv4-IgG1-F194
hsIL-6R+Fv4-IgG1-F196
hsIL-6R+Fv4-IgG1-F198
hsIL-6R+Fv4-IgG1-F262
hsIL-6R+Fv4-IgG1-F264
hsIL-6R+Fv4-IgG1-F393
hsIL-6R+Fv4-IgG1-F424
hsIL-6R+Fv4-IgG1-F447
100
10
1
0.1
0.01
0
7
14
Time (day)
Plasma antibody concentration (μg/mL)

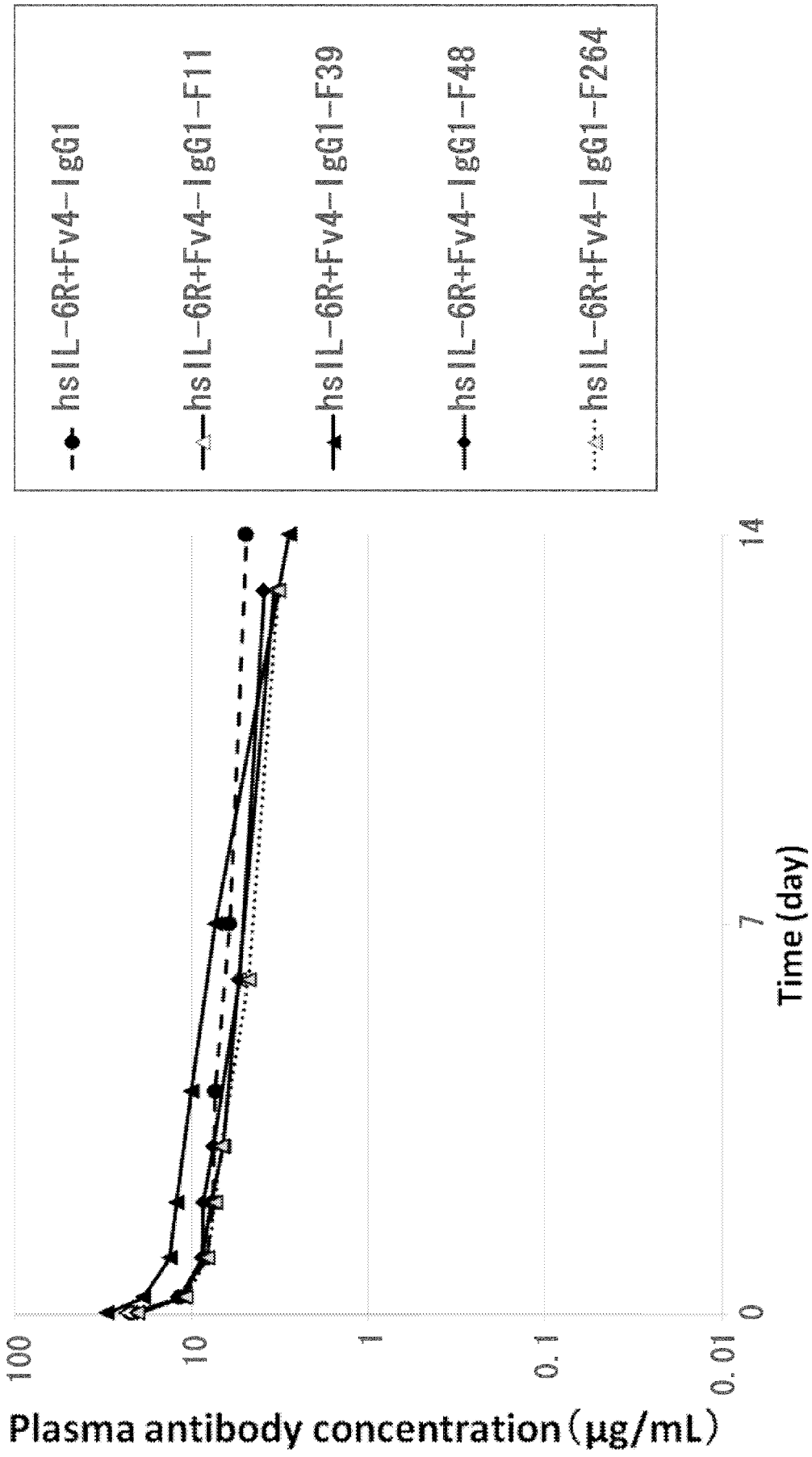
[Fig. 23]


Fv4-IgG1
Fv4-IgG1-F11
Fv4-IgG1-F14
Fv4-IgG1-F39
Fv4-IgG1-F48
Fv4-IgG1-F140
Fv4-IgG1-F157
Fv4-IgG1-F194
Fv4-IgG1-F196
Fv4-IgG1-F198
Fv4-IgG1-F262
Fv4-IgG1-F264
Fv4-IgG1-F393
Fv4-IgG1-F424
Fv4-IgG1-F447
1
0.1
0.01
0.001
0
7
14
Time (day)
Molar antigen/antibody ratio (value C)

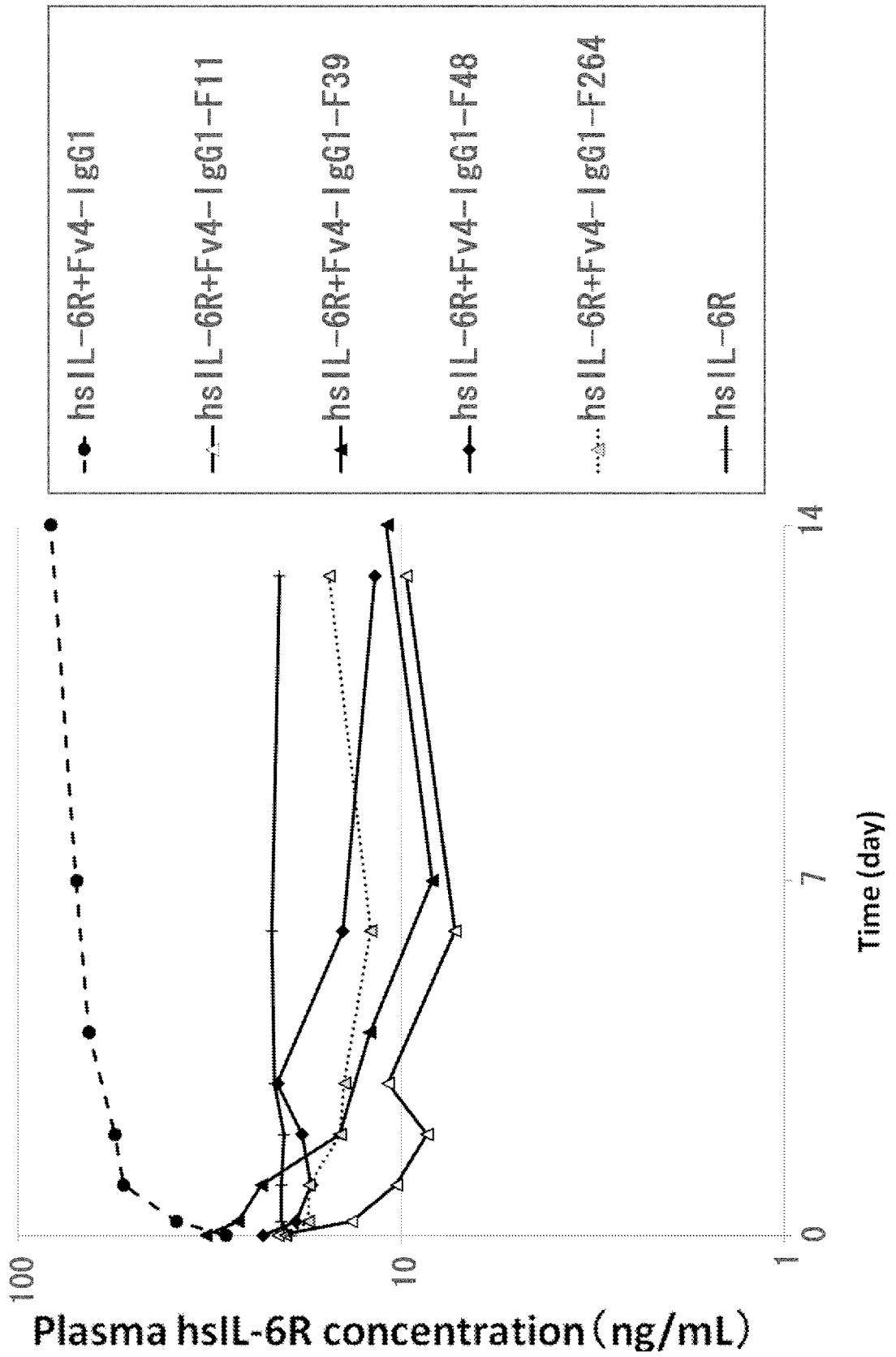
[Fig. 24]


hsIL-6R+Fv4-IgG1
hsIL-6R+Fv4-IgG1-F11
hsIL-6R+Fv4-IgG1-F14
hsIL-6R+Fv4-IgG1-F39
hsIL-6R+Fv4-IgG1-F48
hsIL-6R+Fv4-IgG1-F140
hsIL-6R+Fv4-IgG1-F157
hsIL-6R+Fv4-IgG1-F194
hsIL-6R+Fv4-IgG1-F196
hsIL-6R+Fv4-IgG1-F198
hsIL-6R+Fv4-IgG1-F262
hsIL-6R+Fv4-IgG1-F264
hsIL-6R+Fv4-IgG1-F393
hsIL-6R+Fv4-IgG1-F424
hsIL-6R+Fv4-IgG1-F447
0.1
0.01
0.001
1.0E-03
1.0E-04
1.0E-05
1.0E-06
1.0E-07
1.0E-08
KD (M) at pH7.0
Molar antigen/antibody ratio (value C)

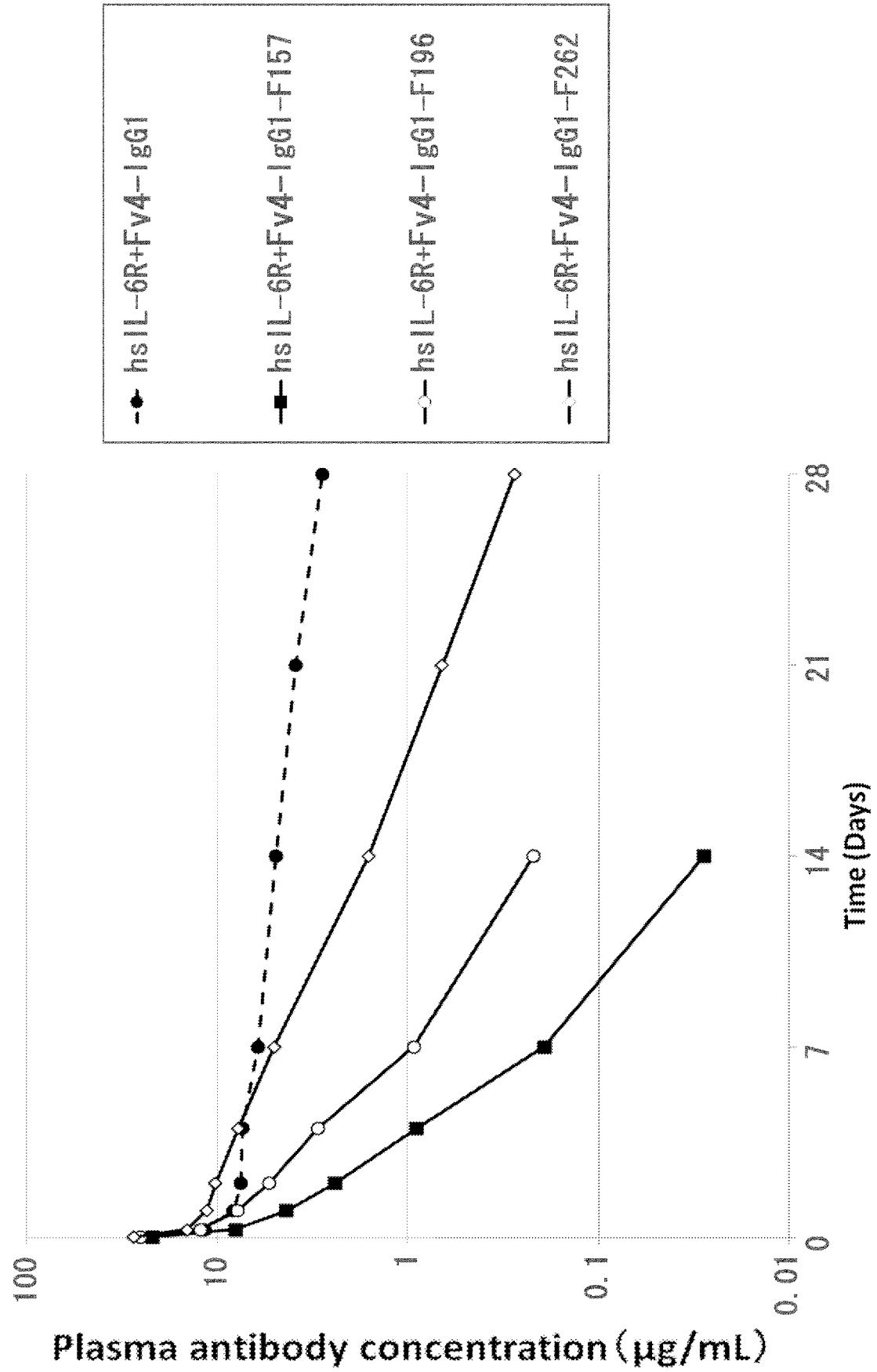
[Fig. 25]


hsIL-6R+Fv4-IgG1
hsIL-6R+Fv4-IgG1-F11
hsIL-6R+Fv4-IgG1-F39
hsIL-6R+Fv4-IgG1-F48
hsIL-6R+Fv4-IgG1-F264
100
10
1
0.1
0.01
0
7
14
Time (day)
Plasma antibody concentration (μg/mL)

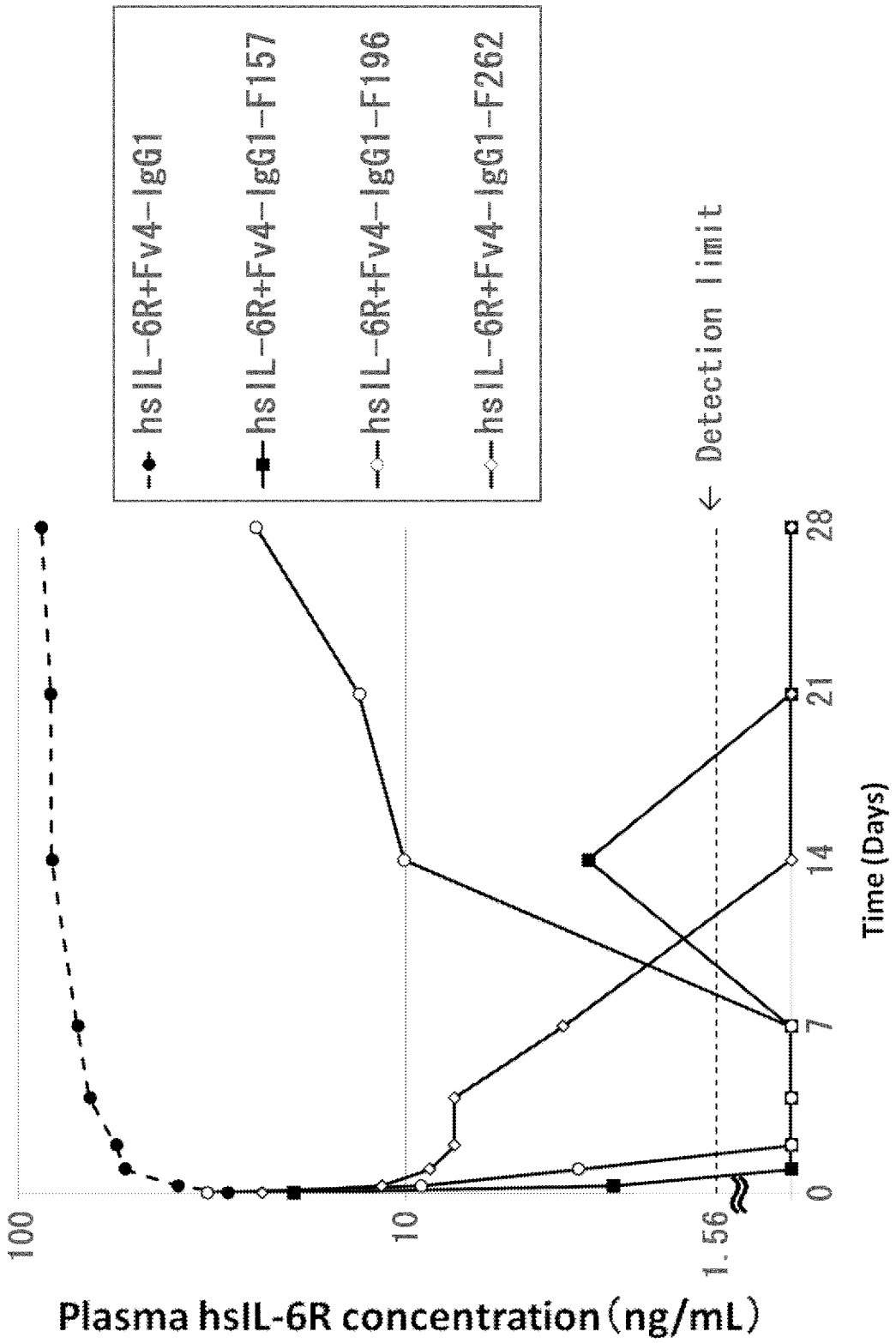
[Fig. 26]


hsIL-6R+Fv4-IgG1
hsIL-6R+Fv4-IgG1-F11
hsIL-6R+Fv4-IgG1-F39
hsIL-6R+Fv4-IgG1-F48
hsIL-6R+Fv4-IgG1-F264
hsIL-6R
100
10
1
0
7
14
Time (day)
Plasma hsIL-6R concentration (ng/mL)

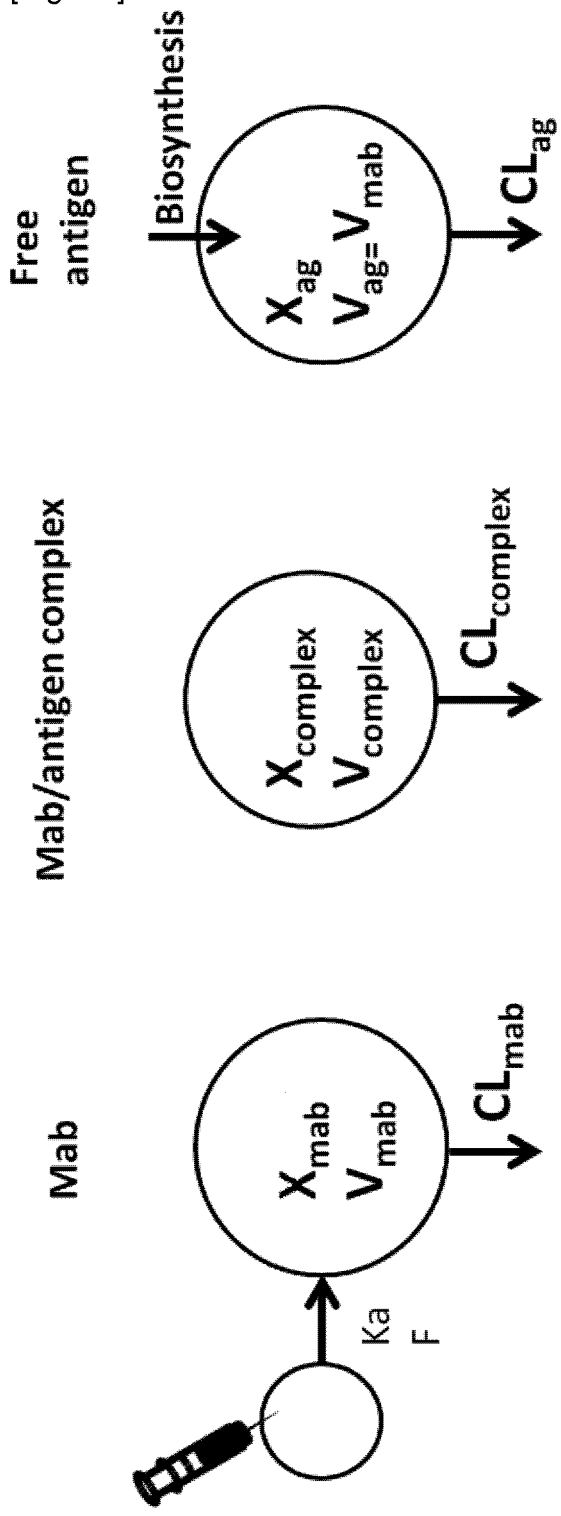
[Fig. 27]


hsIL-6R+Fv4-IgG1
hsIL-6R+Fv4-IgG1-F157
hsIL-6R+Fv4-IgG1-F196
hsIL-6R+Fv4-IgG1-F262
100
10
1
0.1
0.01
0
7
14
21
28
Time (Days)
Plasma antibody concentration (μg/mL)

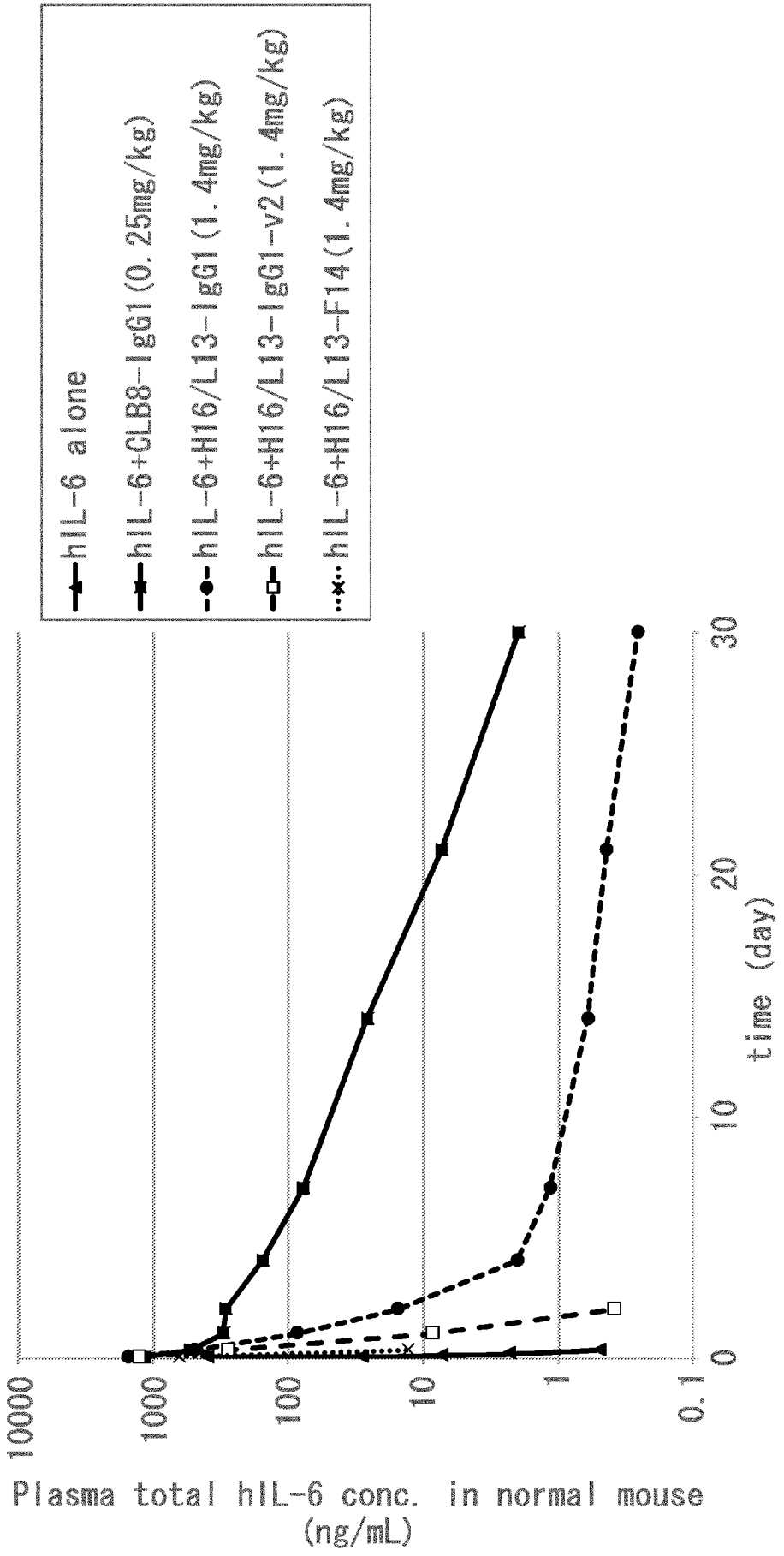
[Fig. 28]


hsIL-6R+Fv4-IgG1
hsIL-6R+Fv4-IgG1-F157
hsIL-6R+Fv4-IgG1-F196
hsIL-6R+Fv4-IgG1-F262
Detection limit
100
10
1.56
0
7
14
21
28
Time (Days)
Plasma hsIL-6R concentration (ng/mL)

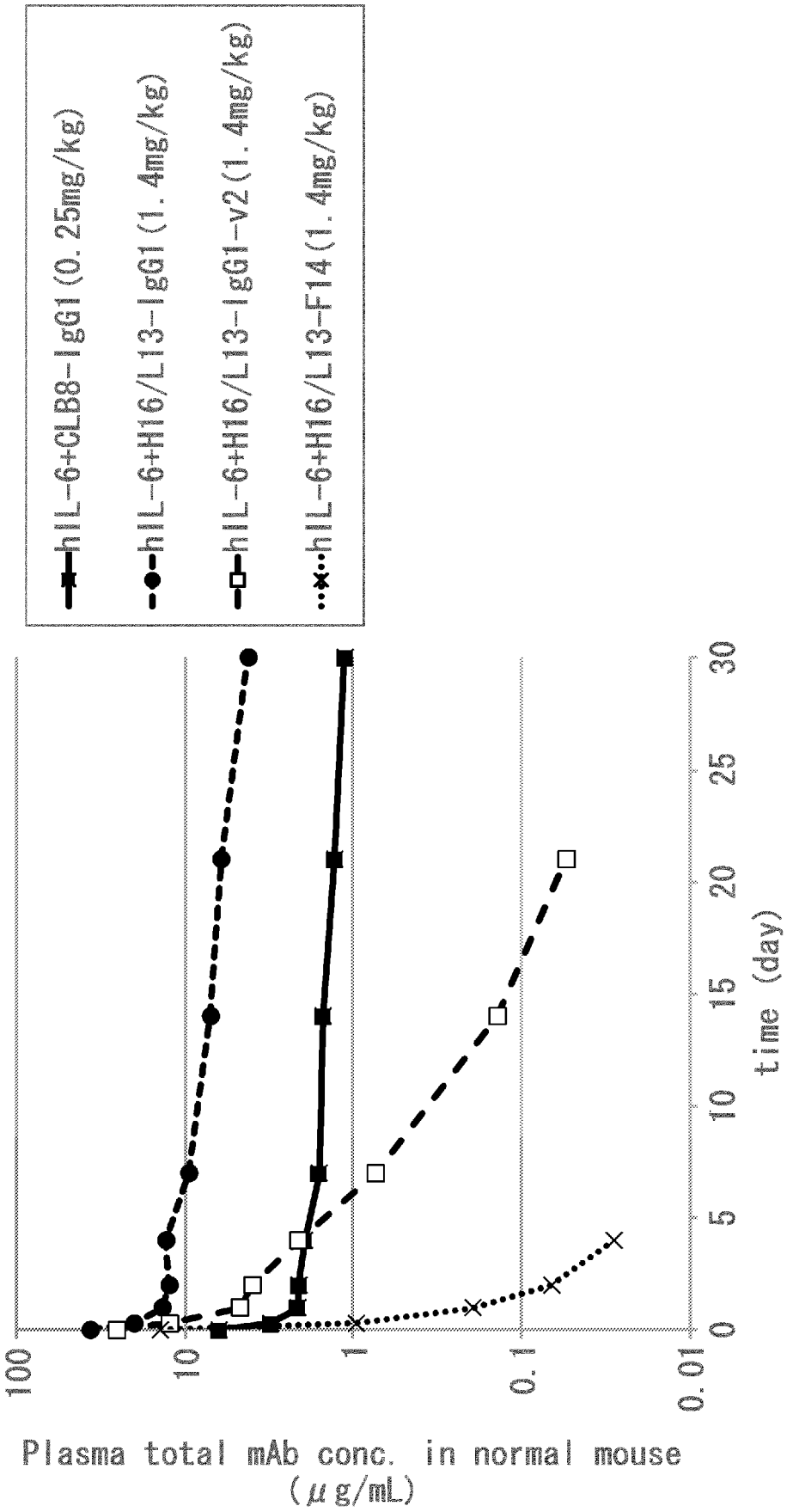
[Fig. 29]


Free antigen
Biosynthesis
X_{ag}
V_{ag}= V_{mab}
CL_{ag}
Mab/antigen complex
$X_{complex}$
$V_{complex}$
$CL_{complex}$
Mab
X_{mab}
V_{mab}
CL_{mab}
Ka
F

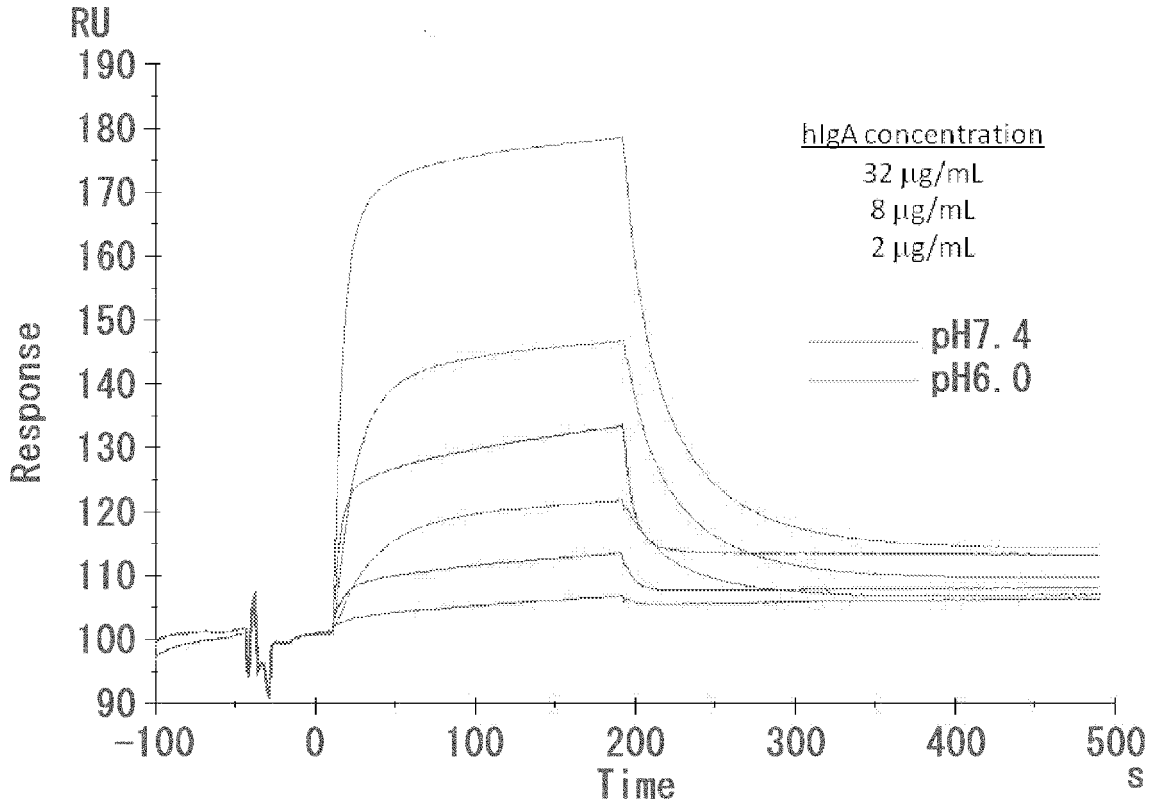
[Fig. 30]


hIL-6 alone
hIL-6+CLB8-IgG1 (0.25mg/kg)
hIL-6+H16/L13-IgG1 (1.4mg/kg)
hIL-6+H16/L13-IgG1-v2 (1.4mg/kg)
hIL-6+H16/L13-F14 (1.4mg/kg)
10000
1000
100
10
1
0.1
0
10
20
30
time (day)
Plasma total hIL-6 conc. in normal mouse (ng/mL)

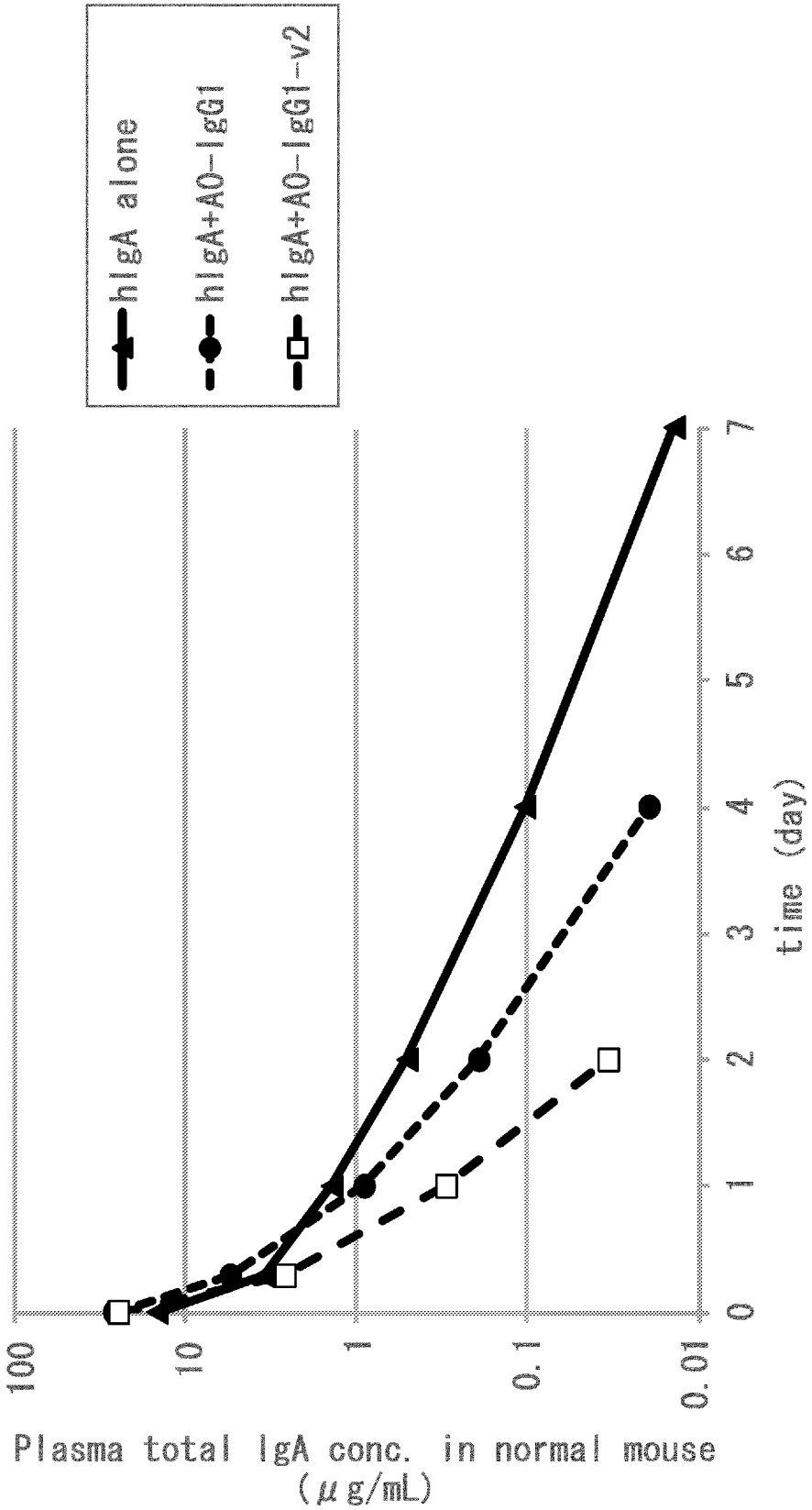
[Fig. 31]


hIL-6+CLB8-IgG1 (0.25mg/kg)
hIL-6+H16/L13-IgG1 (1.4mg/kg)
hIL-6+H16/L13-IgG1-v2 (1.4mg/kg)
hIL-6+H16/L13-F14 (1.4mg/kg)
100
10
1
0.1
0.01
0
5
10
15
20
25
30
time (day)
Plasma total mAb conc. in normal mouse
(μg/mL)

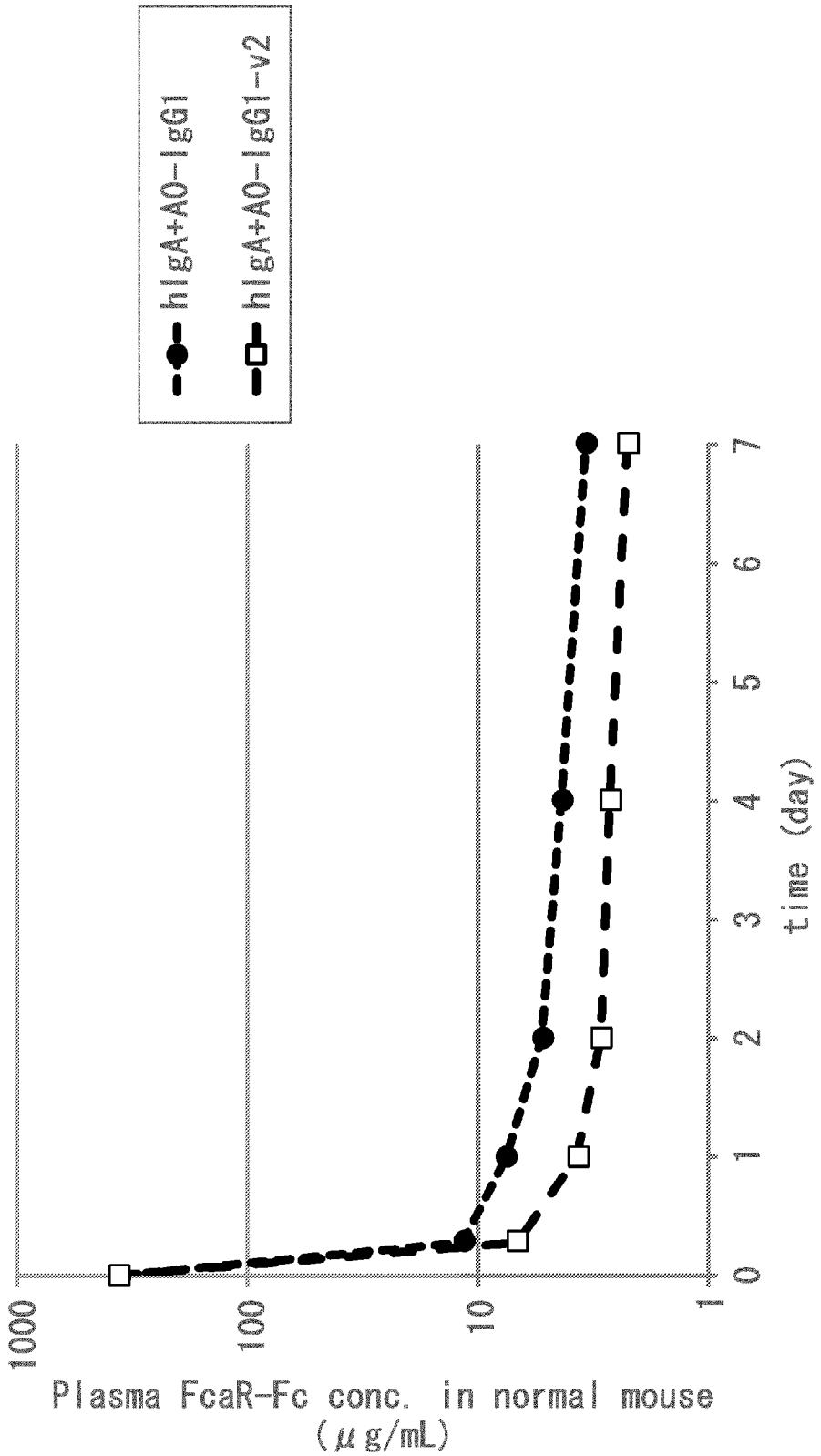
[Fig. 32]


RU
190
180
170
160
150
140
130
120
110
100
90
Response
−100
0
100
200
300
400
500
Time
s
hIgA concentration
32 μg/mL
8 μg/mL
2 μg/mL
pH7. 4
pH6. 0

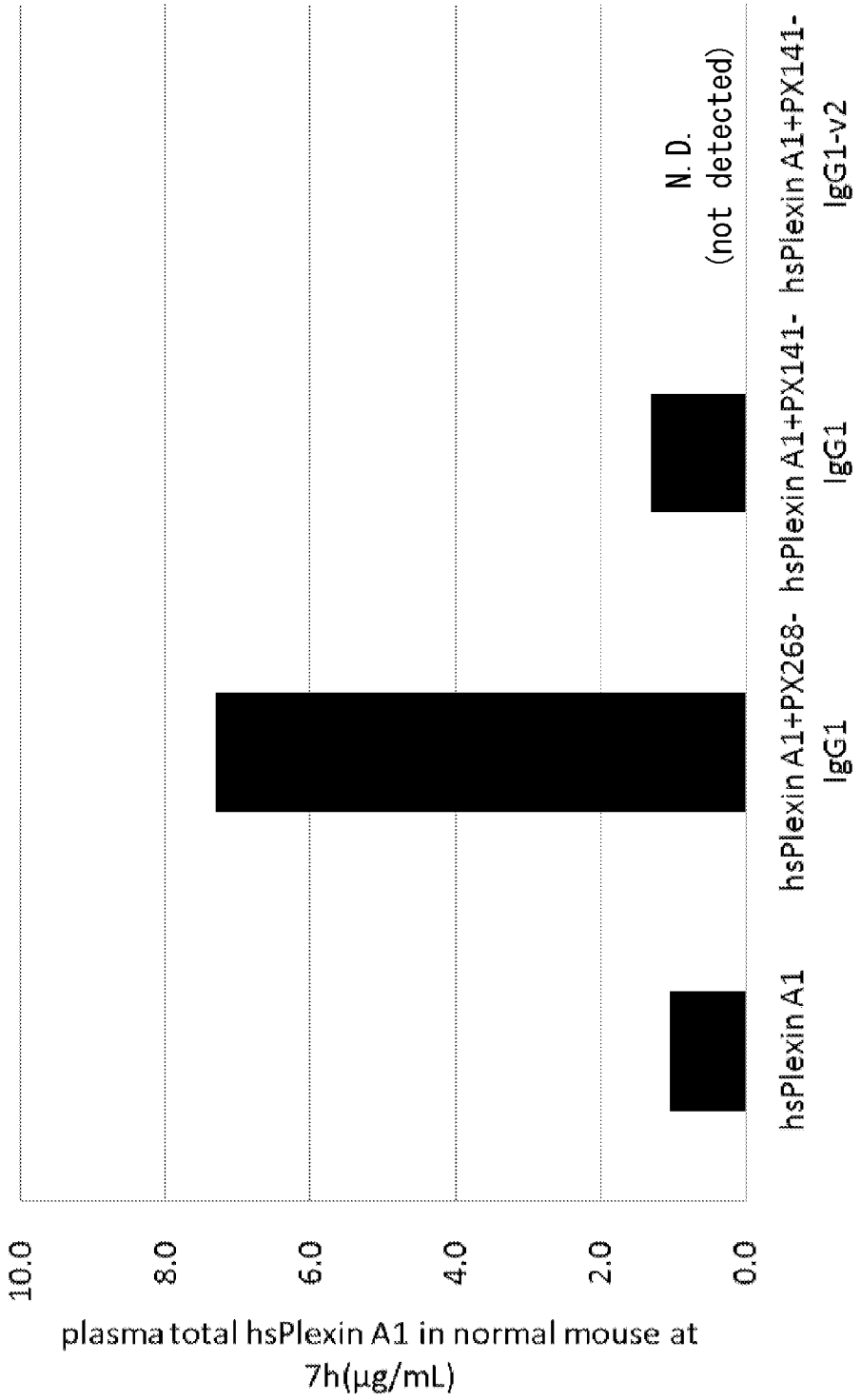
[Fig. 33]


hIgA alone
hIgA+AO-IgG1
hIgA+AO-IgG1-v2
100
10
1
0.1
0.01
0
1
2
3
4
5
6
7
time (day)
Plasma total IgA conc. in normal mouse
(μg/mL)

[Fig. 34]


hIgA+AO-IgG1
hIgA+AO-IgG1-v2
1000
100
10
1
0
1
2
3
4
5
6
7
time (day)
Plasma FcaR-Fc conc. in normal mouse
(μg/mL)

[Fig. 35]


10.0
8.0
6.0
4.0
2.0
0.0
plasma total hsPlexin A1 in normal mouse at 7h(μg/mL)
hsPlexin A1
hsPlexin A1+PX268-IgG1
hsPlexin A1+PX141-IgG1
N. D. (not detected)
hsPlexin A1+PX141-IgG1-v2