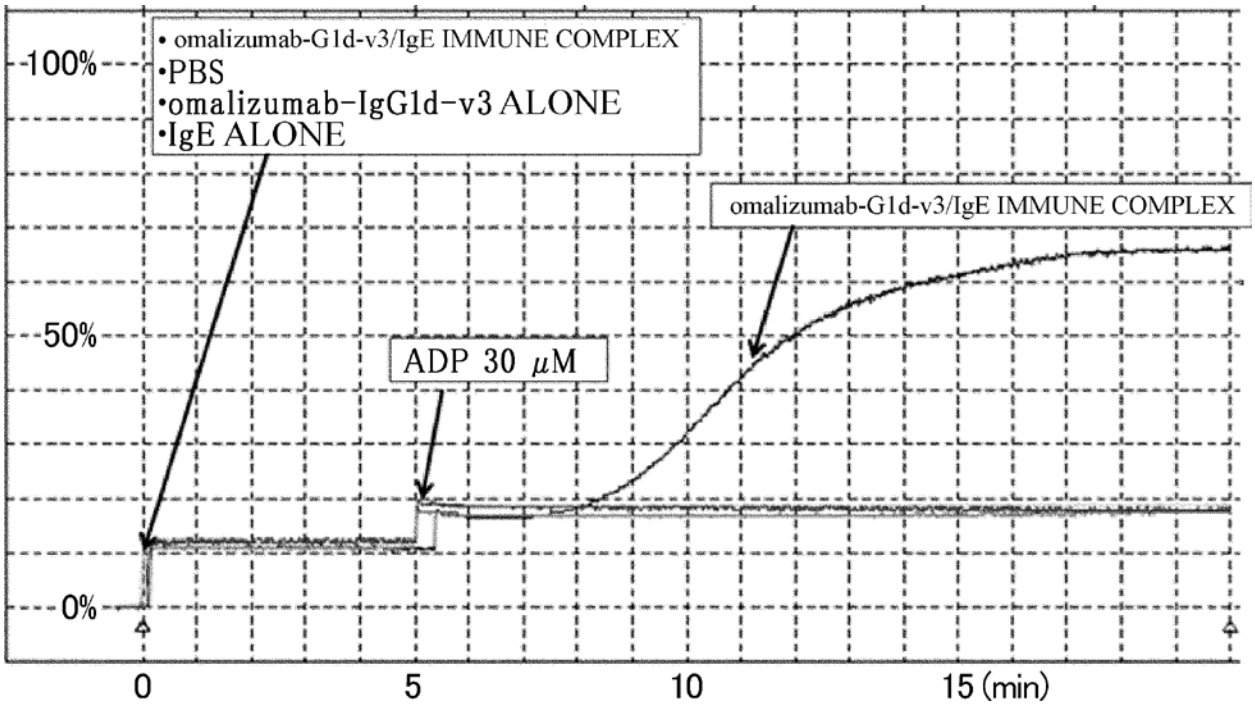

• omalizumab-G1d-v3/IgE IMMUNE COMPLEX
•PBS
•omalizumab-IgG1d-v3 ALONE
•IgE ALONE
omalizumab-G1d-v3/IgE IMMUNE COMPLEX
ADP 30 μM
100%
50%
0%
0
5
10
15 (min)

FIG. 1

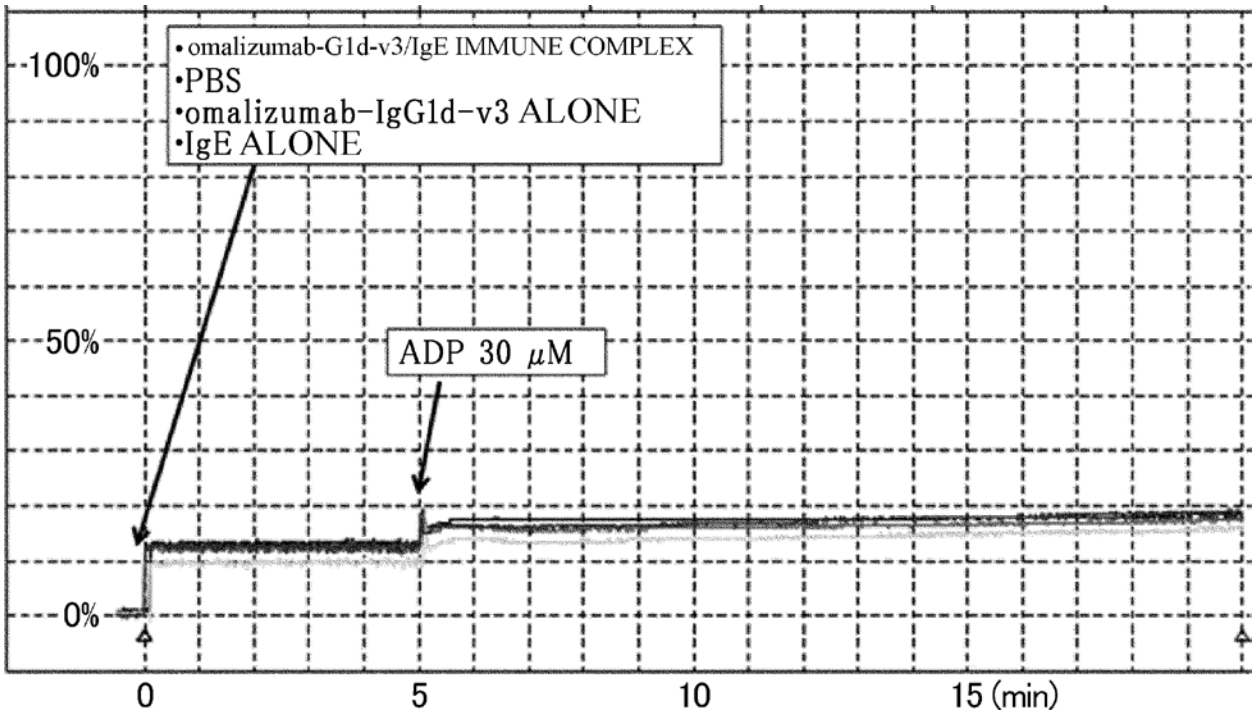

• omalizumab-G1d-v3/IgE IMMUNE COMPLEX
•PBS
•omalizumab-IgG1d-v3 ALONE
•IgE ALONE
ADP 30 μM
100%
50%
0%
0
5
10
15 (min)

FIG. 2

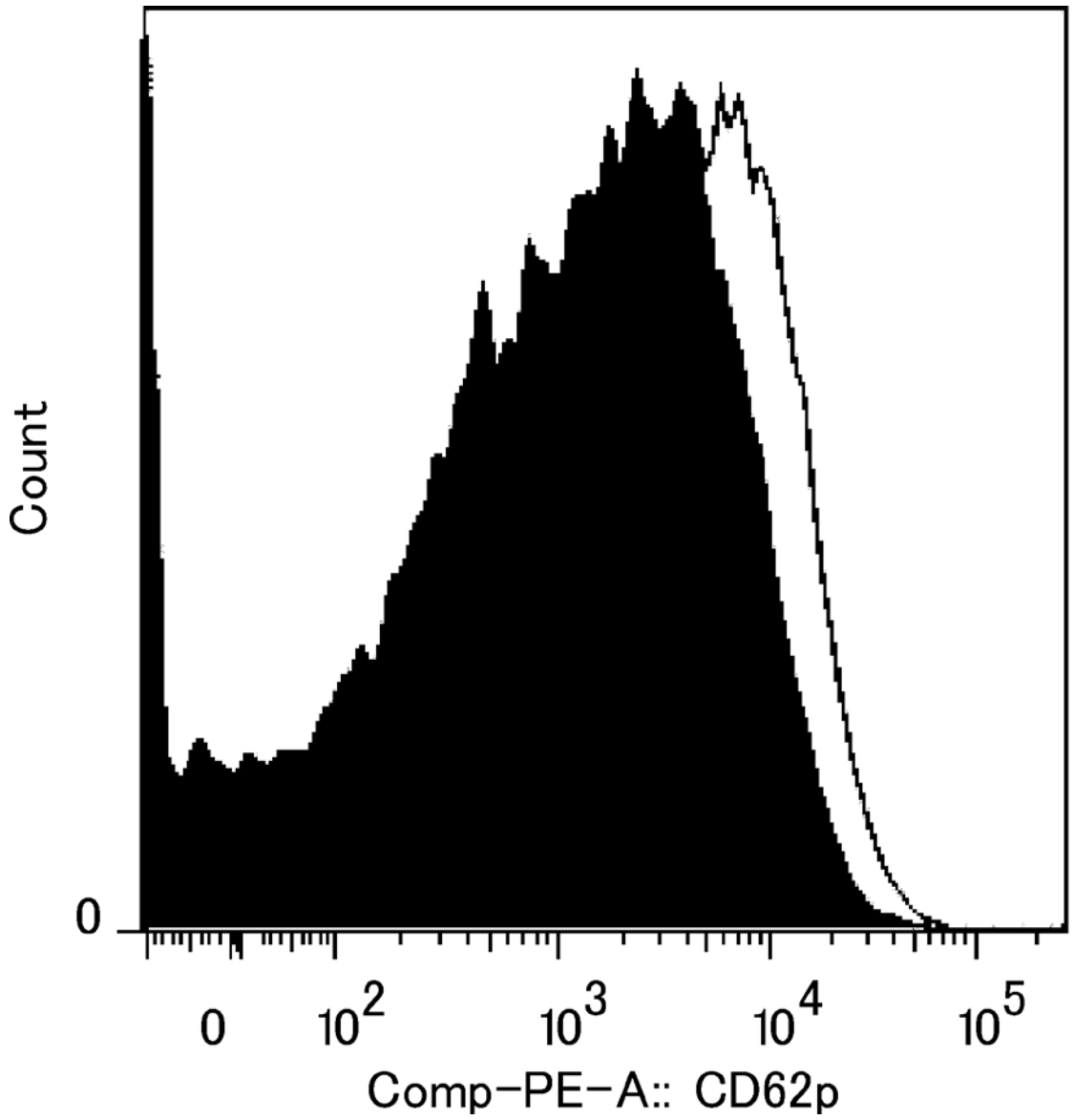


FIG. 3

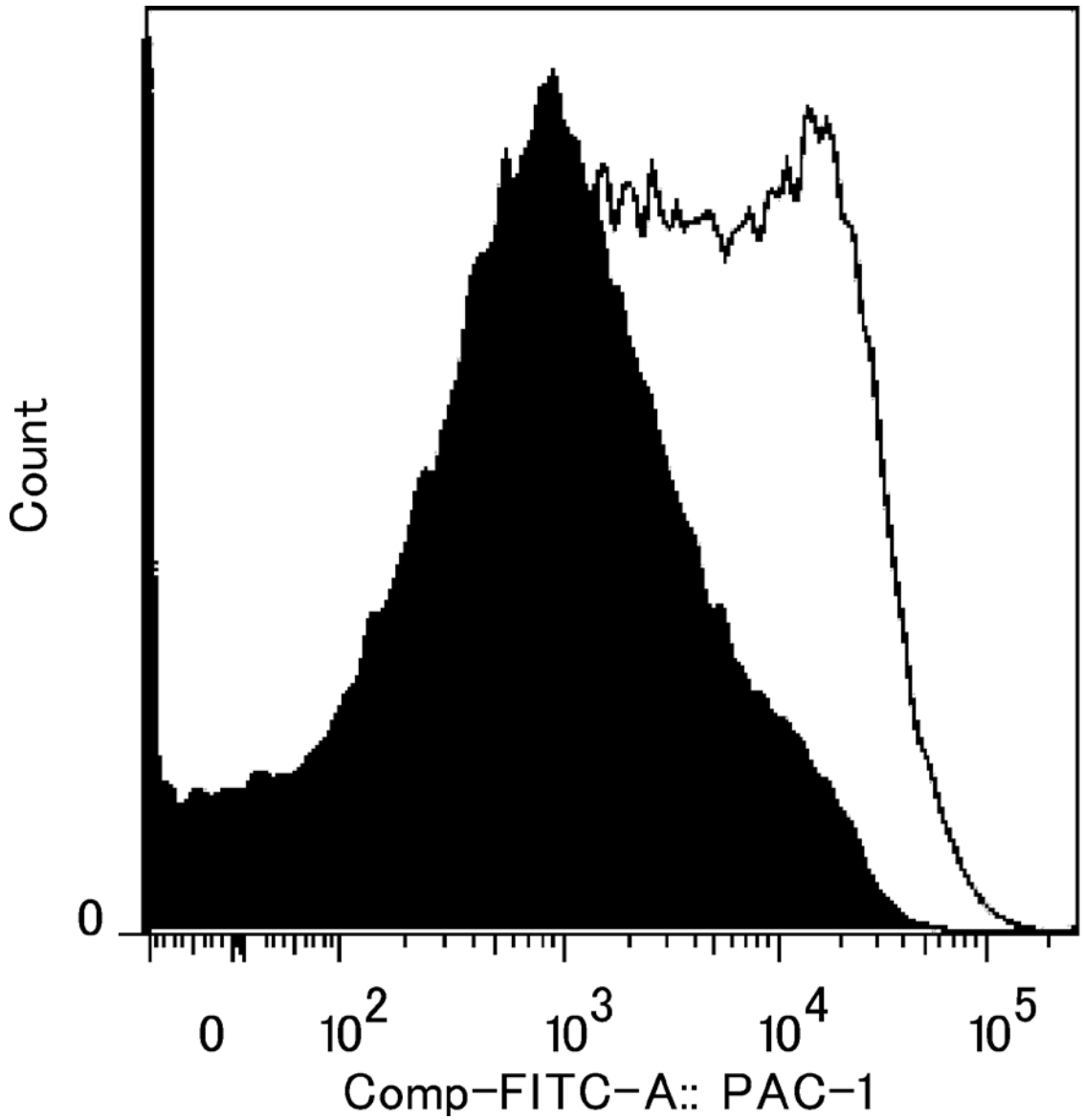


FIG. 4

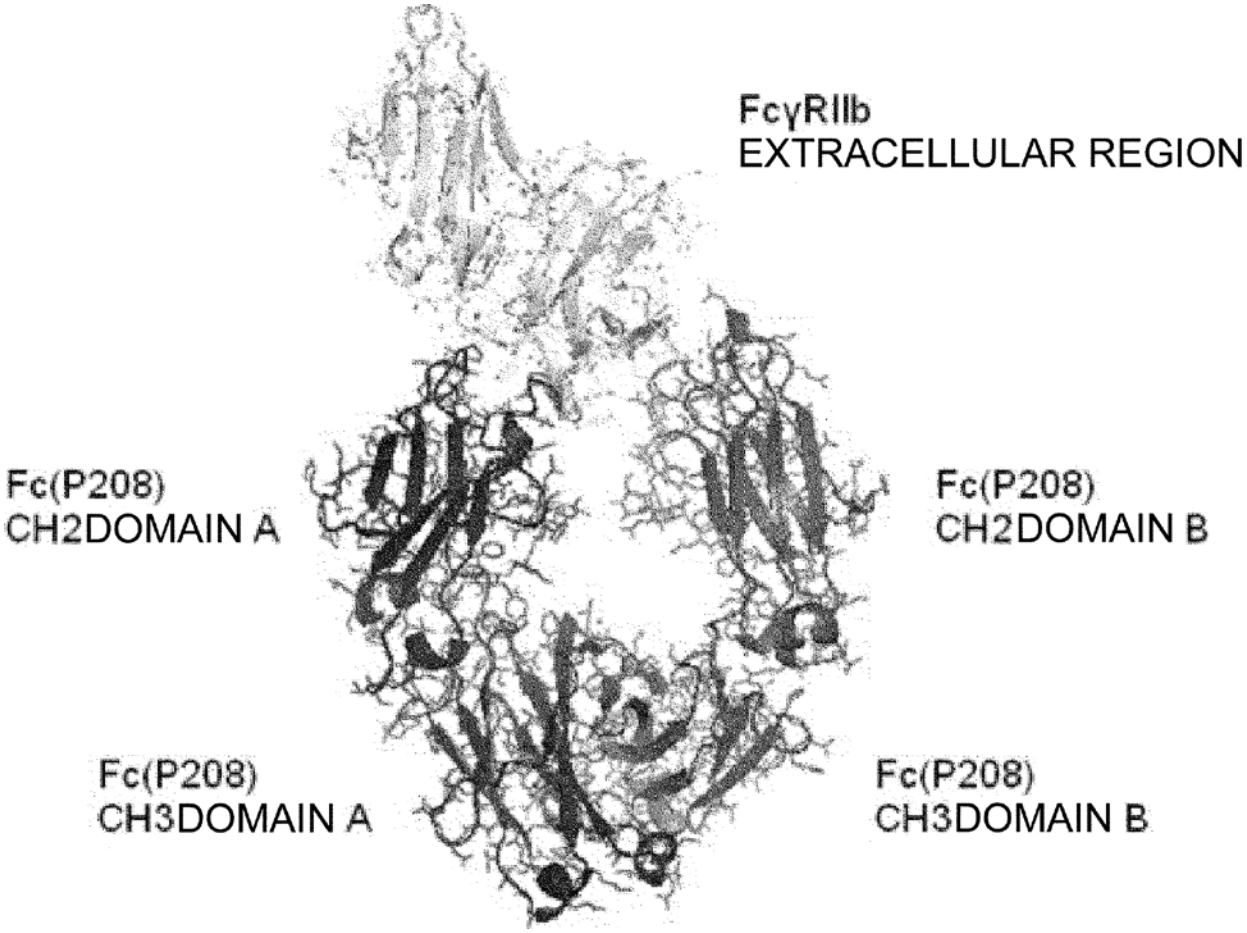

FcγRIIb
EXTRACELLULAR REGION
Fc(P208)
CH2DOMAIN A
Fc(P208)
CH2DOMAIN B
Fc(P208)
CH3DOMAIN A
Fc(P208)
CH3DOMAIN B

FIG. 5

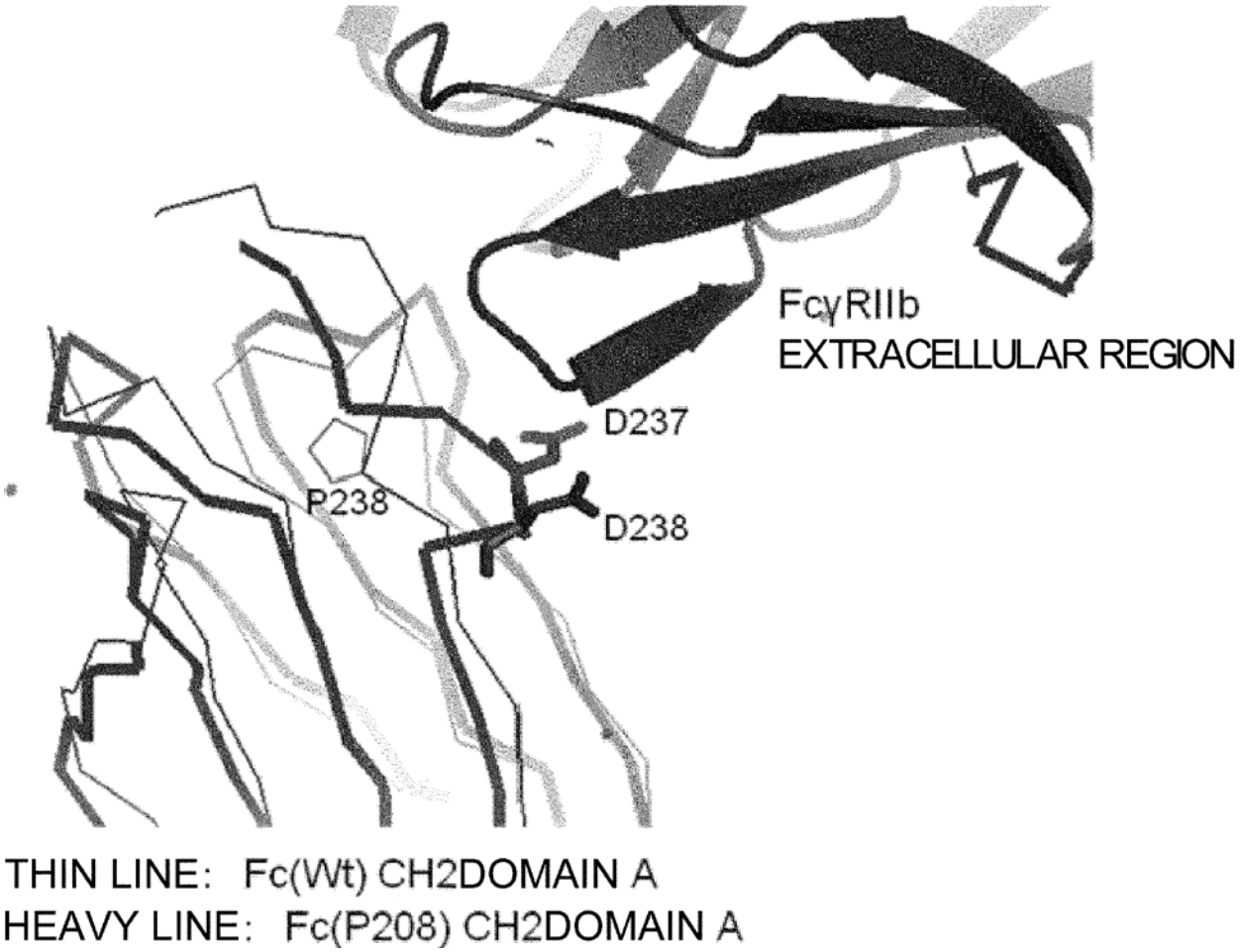

FcγRIIb
EXTRACELLULAR REGION
D237
P238
D238
THIN LINE: Fc(Wt) CH2DOMAIN A
HEAVY LINE: Fc(P208) CH2DOMAIN A

FIG. 6

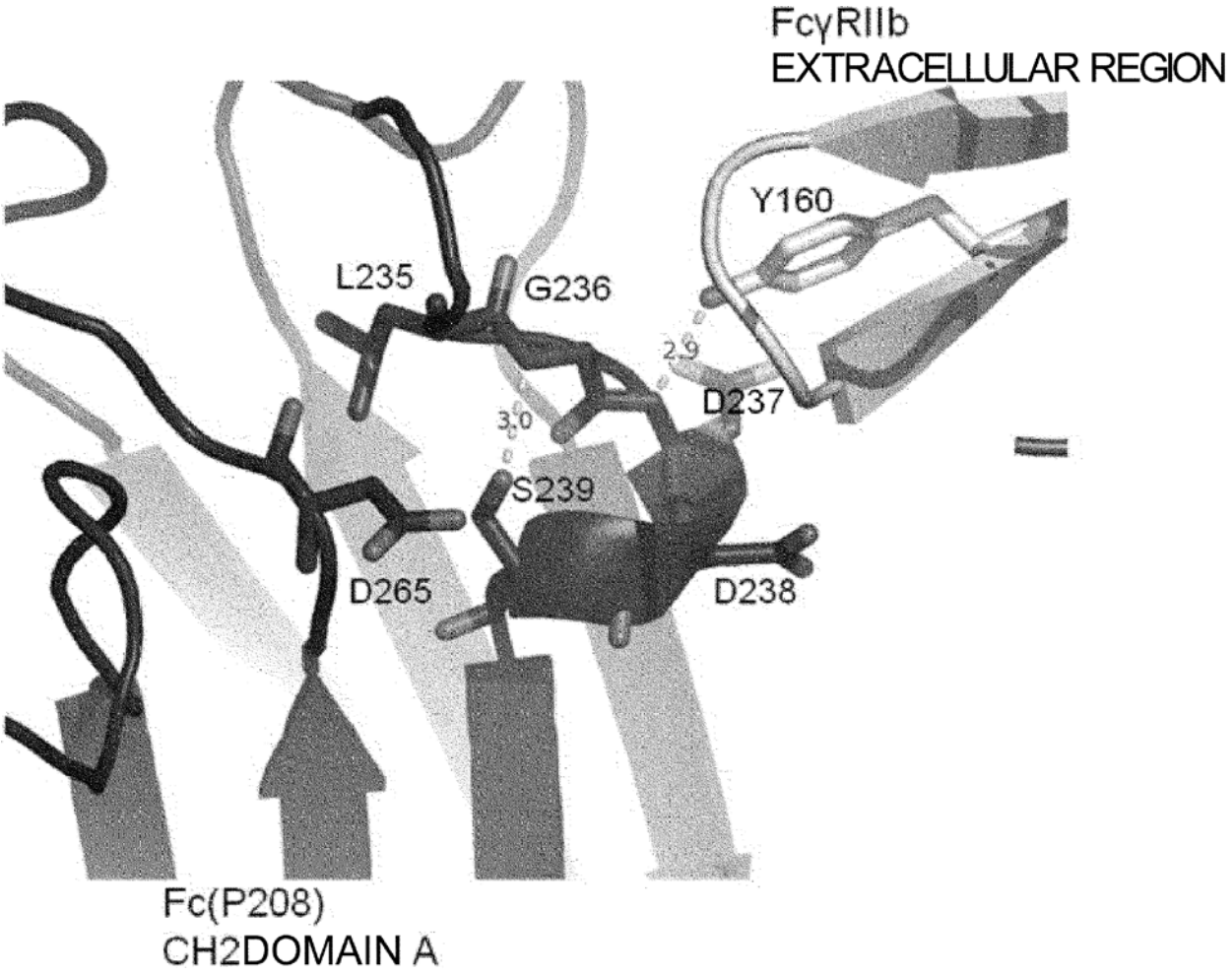

FcγRIIb
EXTRACELLULAR REGION
Y160
L235
G236
2.9
D237
3.0
S239
D265
D238
Fc(P208)
CH2DOMAIN A

FIG. 7

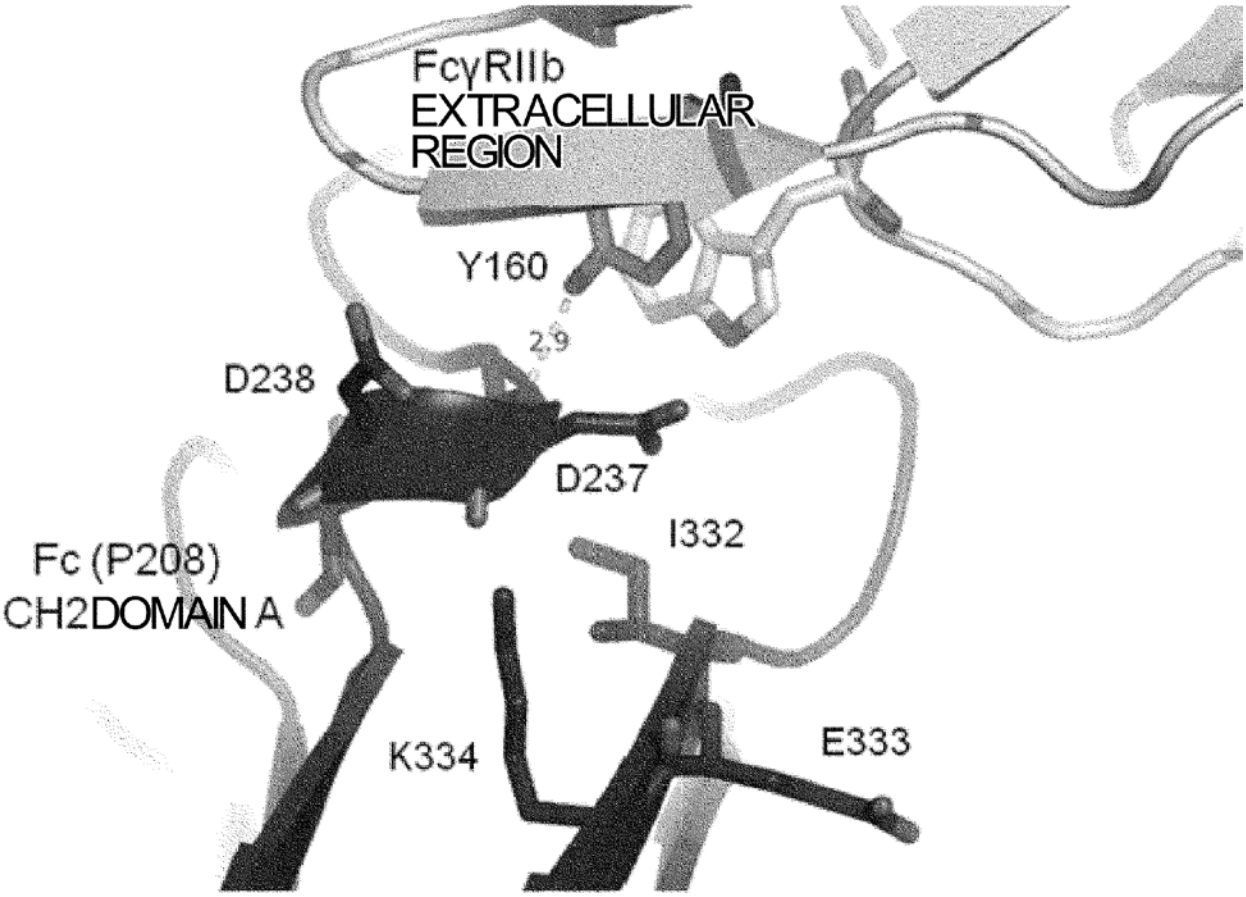
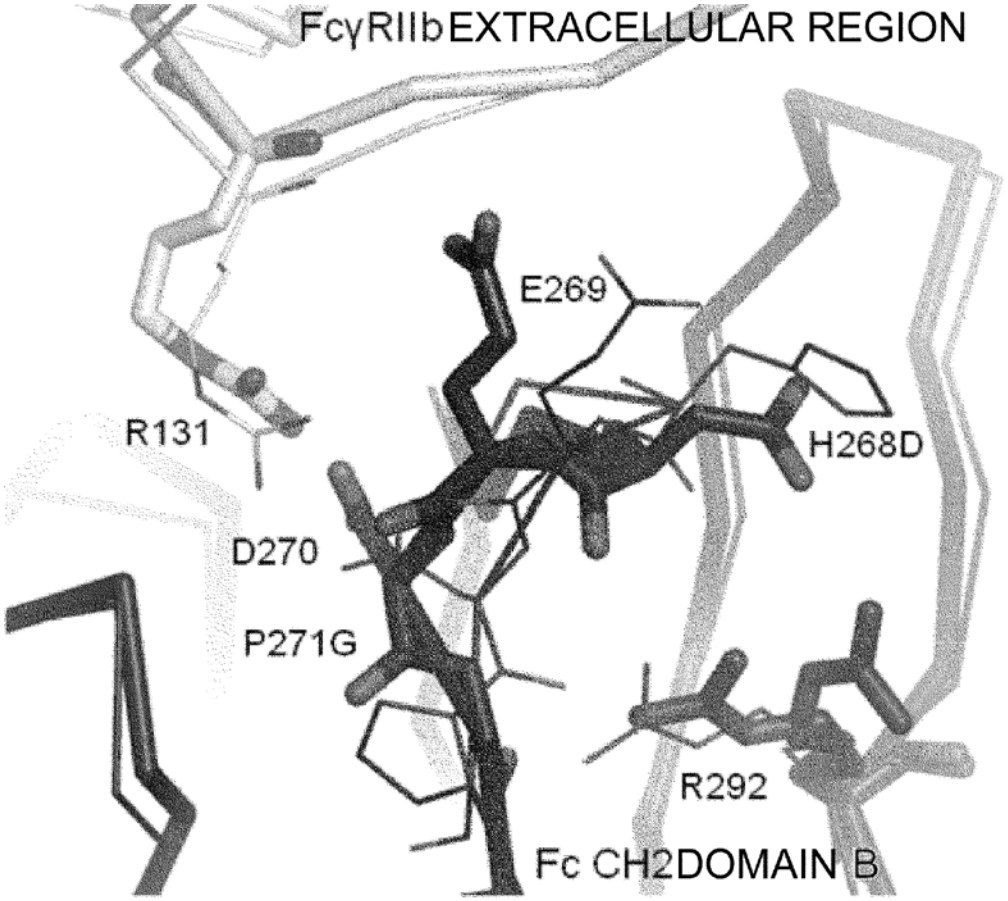
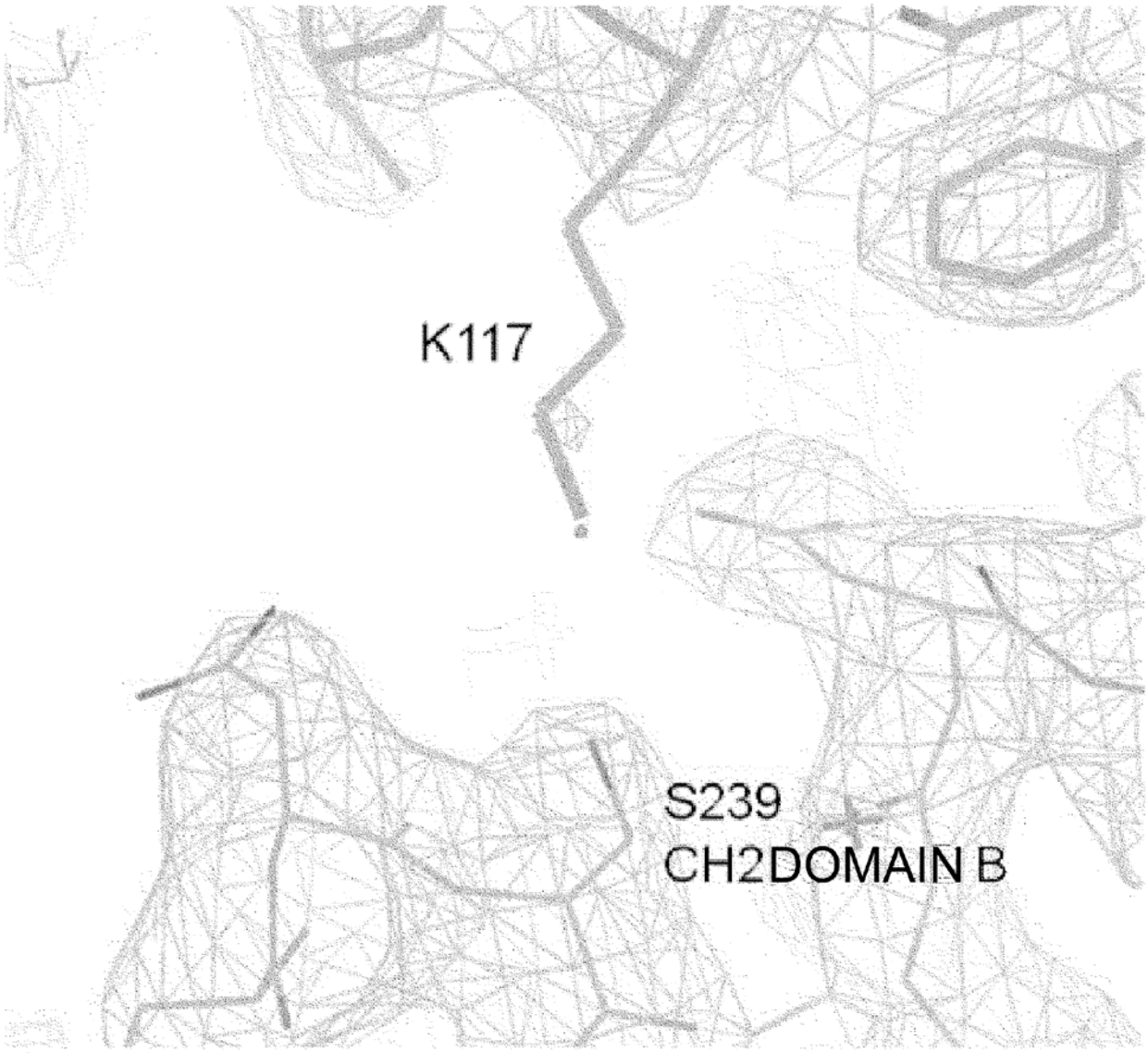

FcγRIIb
EXTRACELLULAR
REGION
Y160
2.9
D238
D237
I332
Fc (P208)
CH2DOMAIN A
K334
E333

FIG. 8



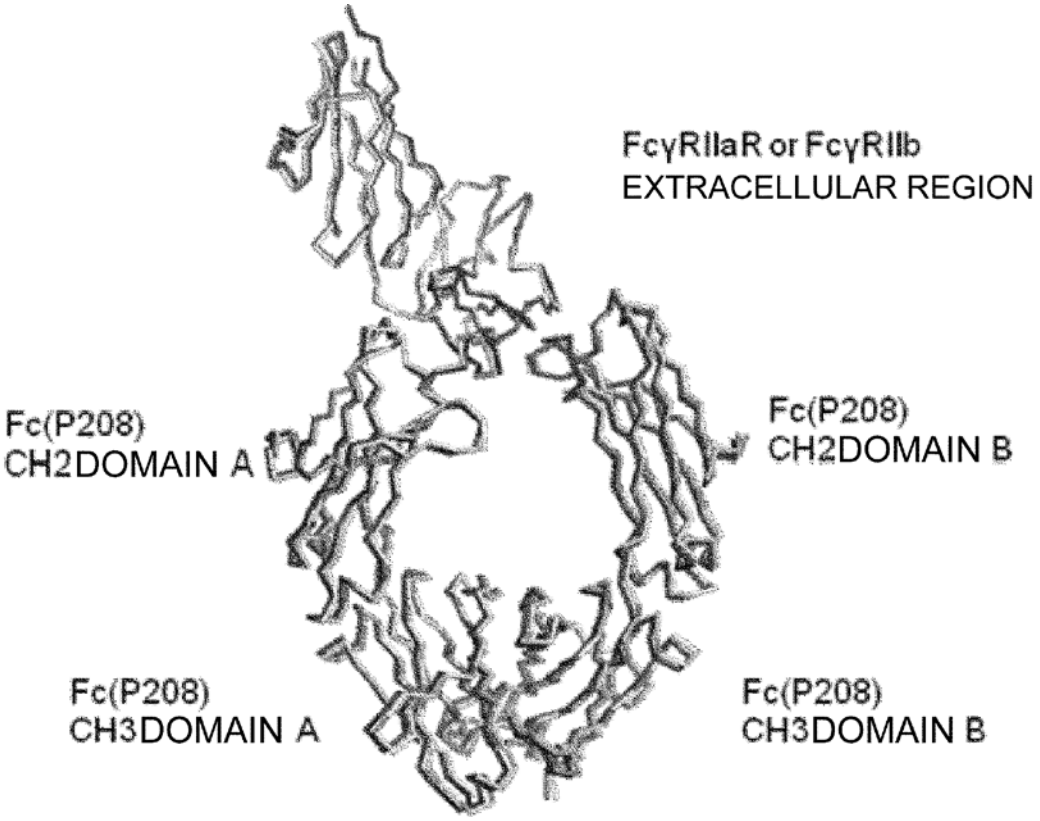
THIN LINE: X-RAY CRYSTAL STRUCTURE OF Fc(P238D)/FcγRIIb EXTRACELLULAR REGION COMPLEX
HEAVY LINE: X-RAY CRYSTAL STRUCTURE OF Fc(P208)/FcγRIIb EXTRACELLULAR REGION COMPLEX

FIG. 9



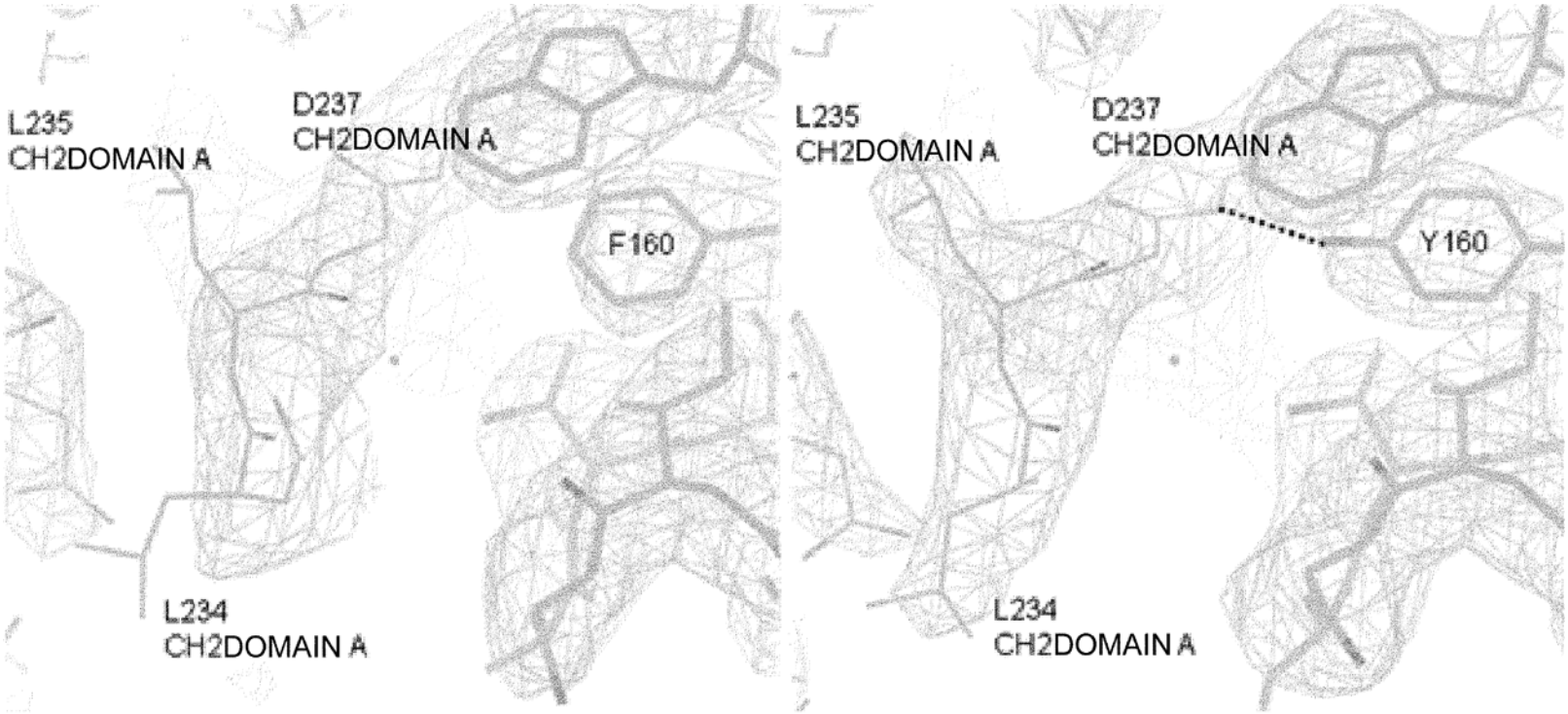
THIN LINE : Fc(P208)
HEAVY LINE : FcγRIIb EXTRACELLULAR REGION

FIG. 10



BLACK: X-RAY CRYSTAL STRUCTURE OF Fc(P208)/FcγRIIaR EXTRACELLULAR REGION COMPLEX
GRAY: X-RAY CRYSTAL STRUCTURE OF Fc(P208)/FcγRIIb EXTRACELLULAR REGION COMPLEX

FIG. 11



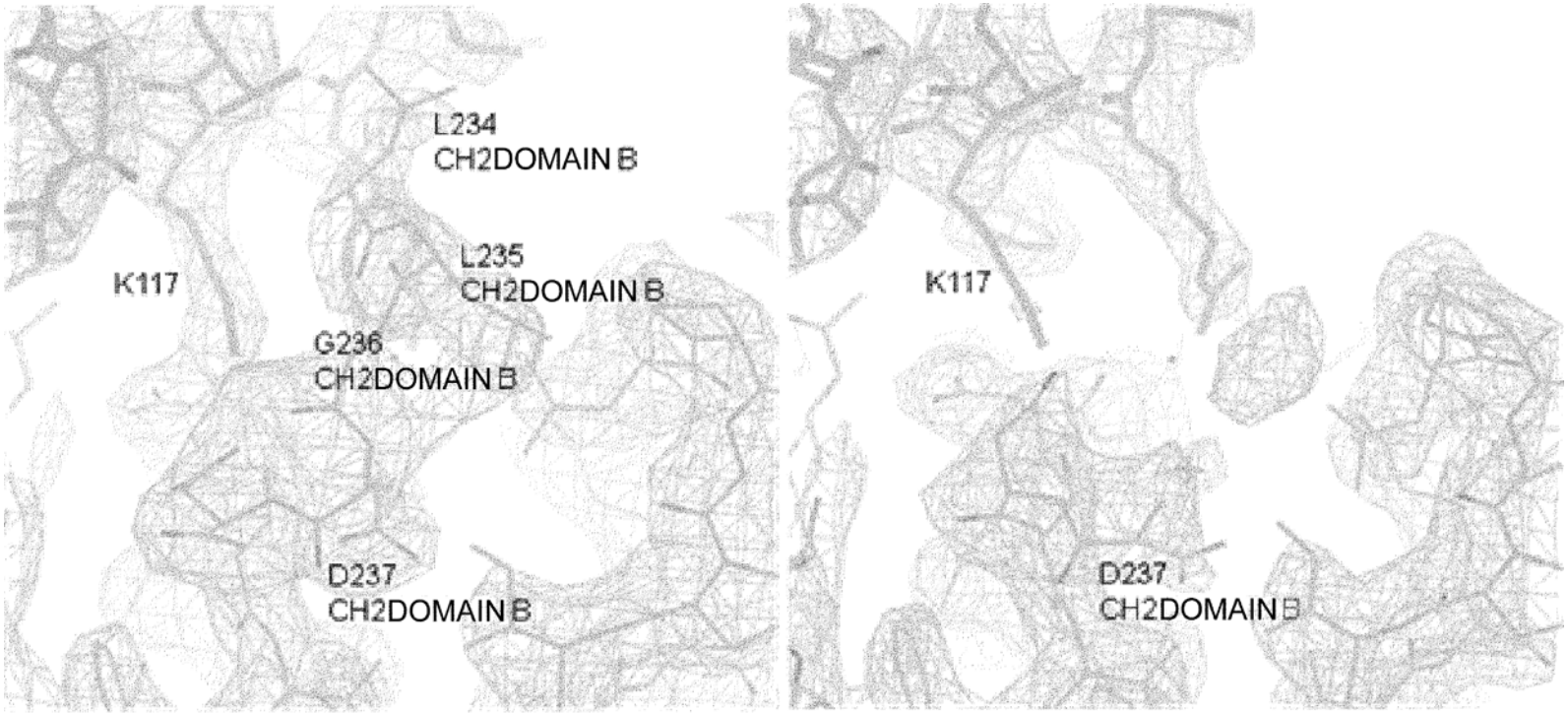
THIN LINE: Fc(P208)

HEAVY LINE: FcγRIIaR or FcγRIIb EXTRACELLULAR REGION

LEFT: X-RAY CRYSTAL STRUCTURE OF Fc(P208)/FcγRIIaR EXTRACELLULAR REGION COMPLEX

RIGHT: X-RAY CRYSTAL STRUCTURE OF Fc(P208)/FcγRIIb EXTRACELLULAR REGION COMPLEX

FIG. 12



THIN LINE: Fc(P208)

HEAVY LINE: FcγRIIaR or FcγRIIb EXTRACELLULAR REGION

LEFT: X-RAY CRYSTAL STRUCTURE OF Fc(P208)/FcγRIIaR EXTRACELLULAR REGION COMPLEX

RIGHT: X-RAY CRYSTAL STRUCTURE OF Fc(P208)/FcγRIIb EXTRACELLULAR REGION COMPLEX

FIG. 13

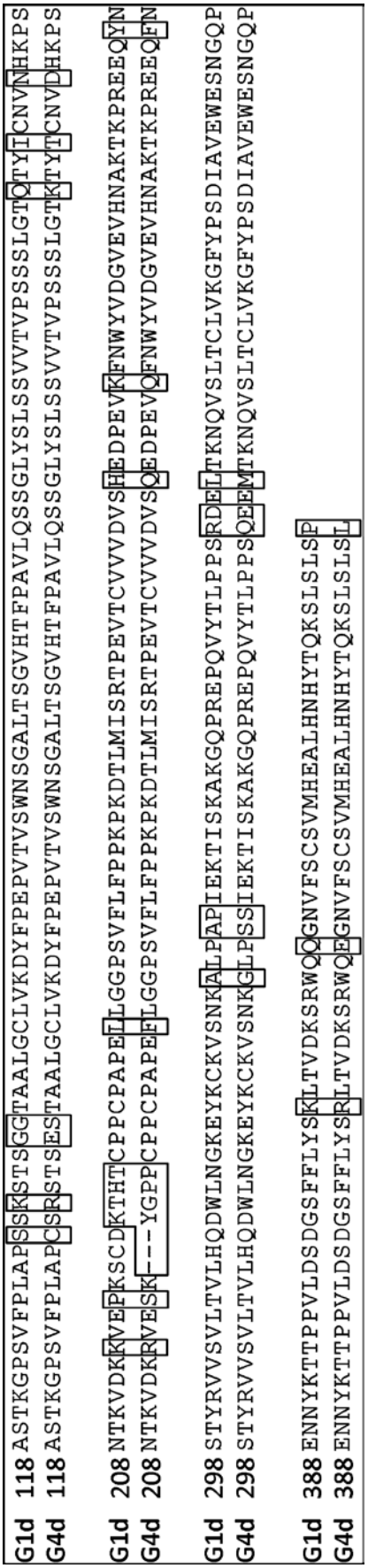

G1d 118 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS
G4d 118 ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS
G1d 208 NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
G4d 208 NTKVDKRVESK---YGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFN
G1d 298 STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP
G4d 298 STYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
G1d 388 ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
G4d 388 ENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSL

FIG. 14

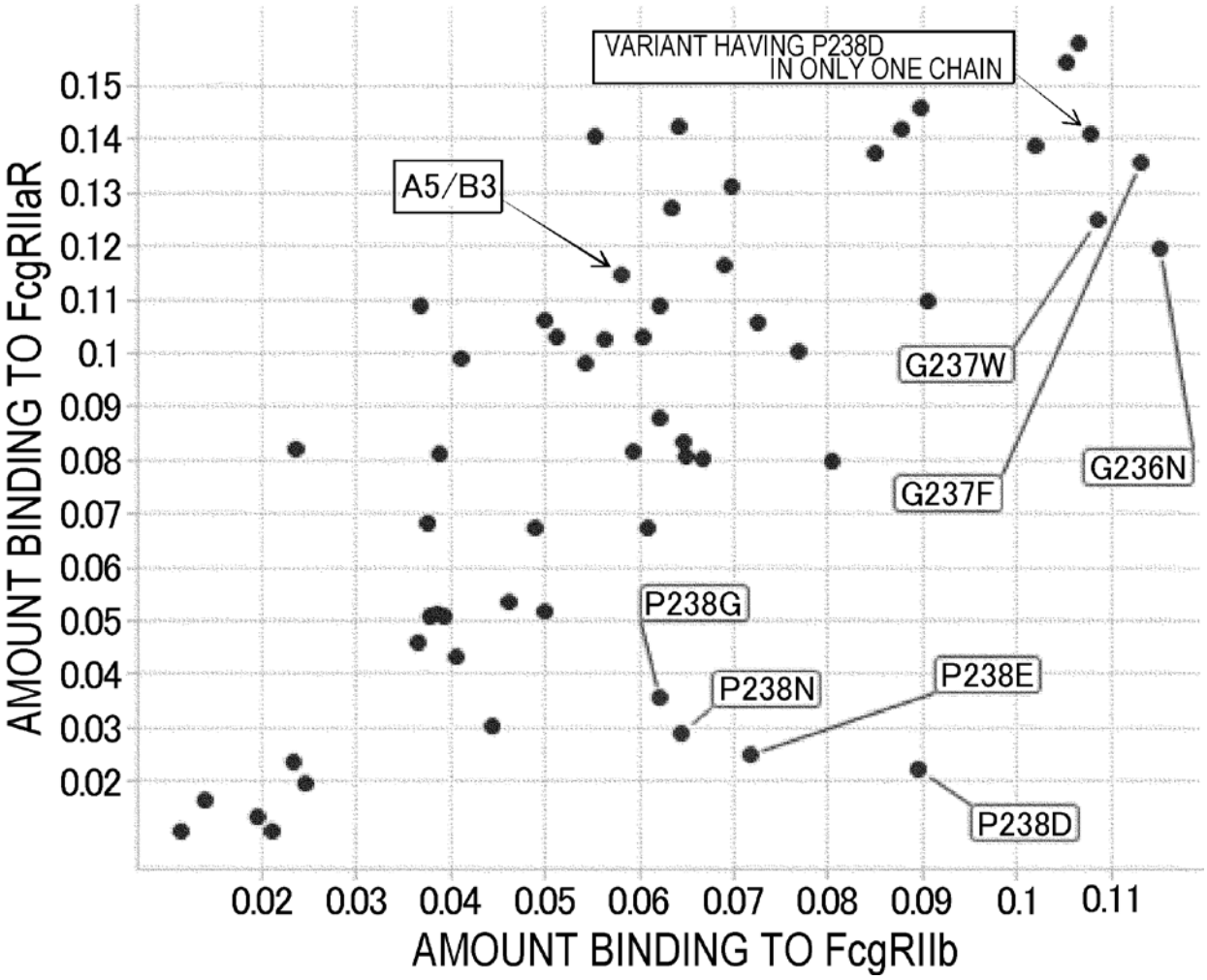

VARIANT HAVING P238D
IN ONLY ONE CHAIN
A5/B3
G237W
G237F
G236N
P238G
P238N
P238E
P238D
AMOUNT BINDING TO FcgRIIaR
AMOUNT BINDING TO FcgRIIb
0.15
0.14
0.13
0.12
0.11
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.02
0.03
0.04
0.05
0.06
0.07
0.08
0.09
0.1
0.11

FIG. 15

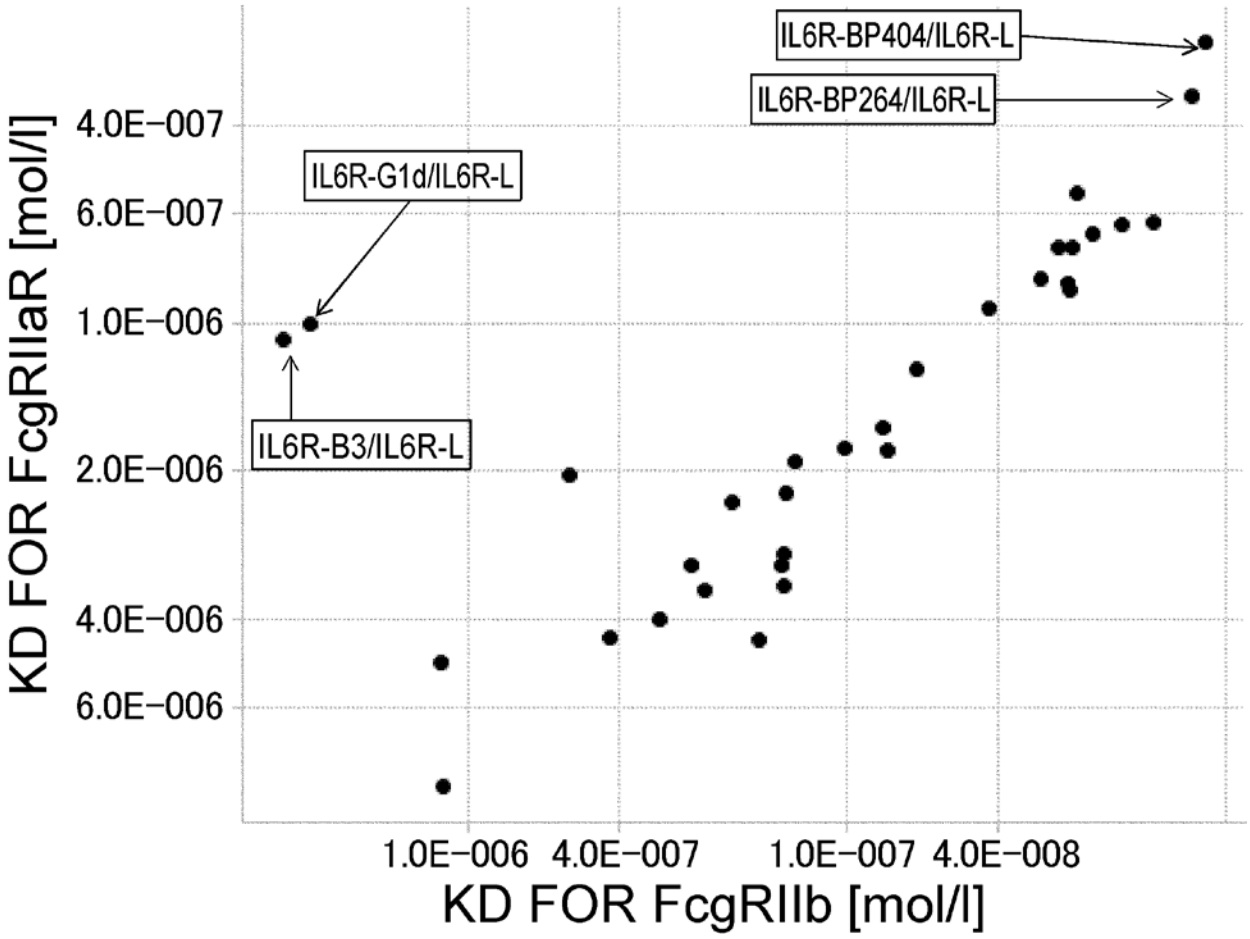

IL6R-BP404/IL6R-L
IL6R-BP264/IL6R-L
IL6R-G1d/IL6R-L
IL6R-B3/IL6R-L
KD FOR FcgRIIaR [mol/l]
4.0E−007
6.0E−007
1.0E−006
2.0E−006
4.0E−006
6.0E−006
1.0E−006
4.0E−007
1.0E−007
4.0E−008
KD FOR FcgRIIb [mol/l]

FIG. 16

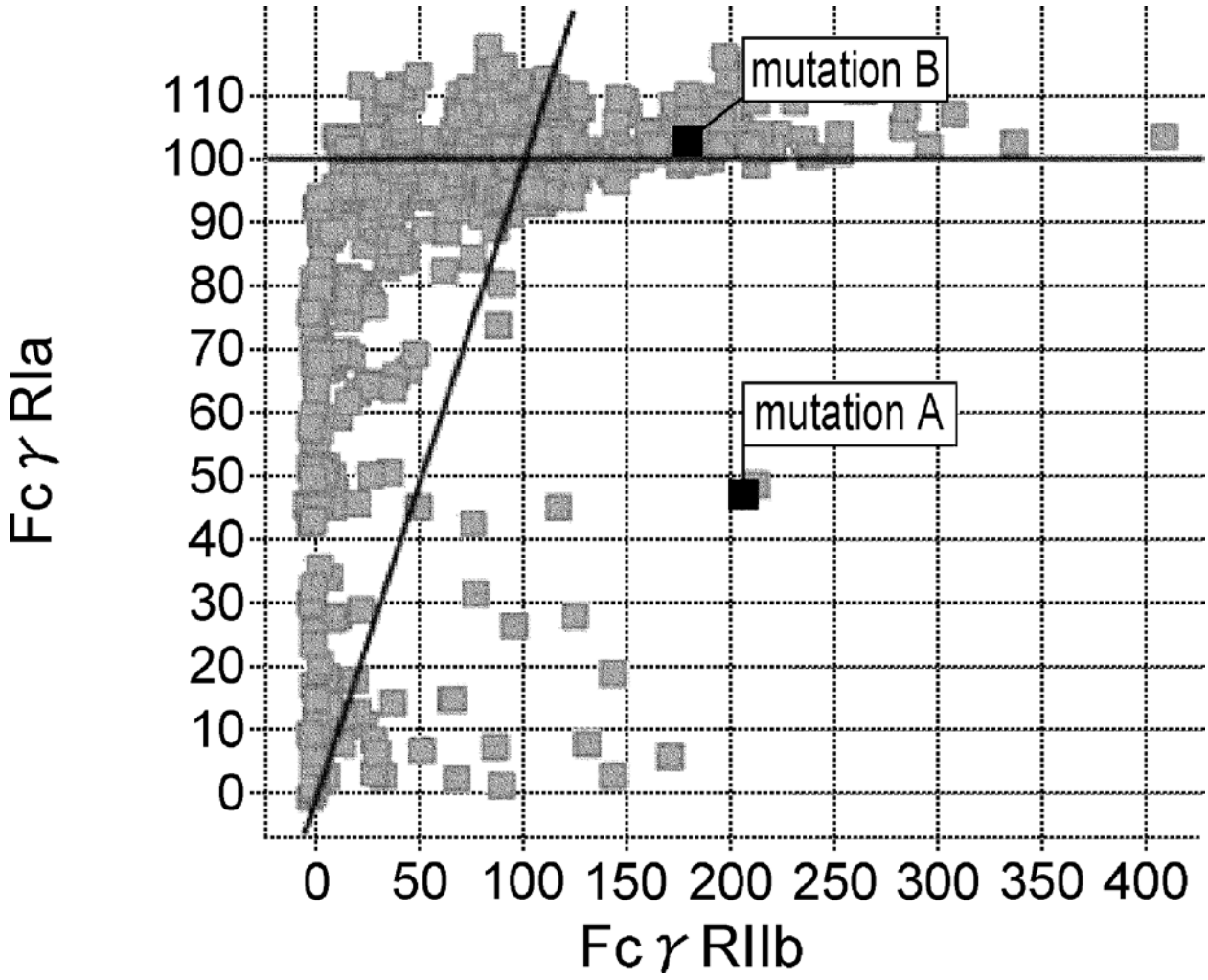

mutation B
mutation A
110
100
90
80
70
60
50
40
30
20
10
0
0 50 100 150 200 250 300 350 400
Fc γ RIIb
Fc γ RIa

FIG. 17

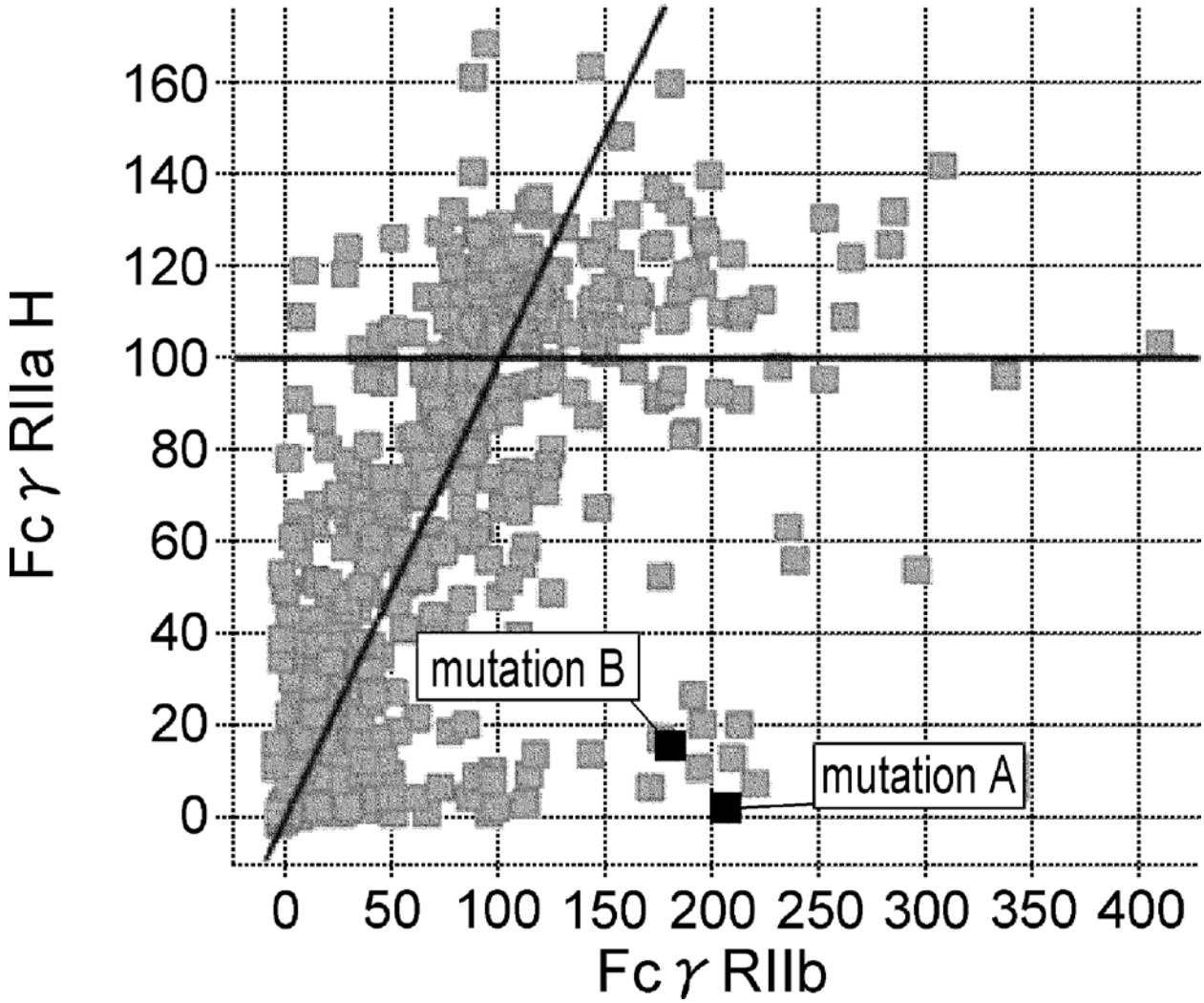

160
140
120
100
80
60
40
20
0
Fc γ RIIa H
mutation B
mutation A
0
50
100
150
200
250
300
350
400
Fc γ RIIb

FIG. 18

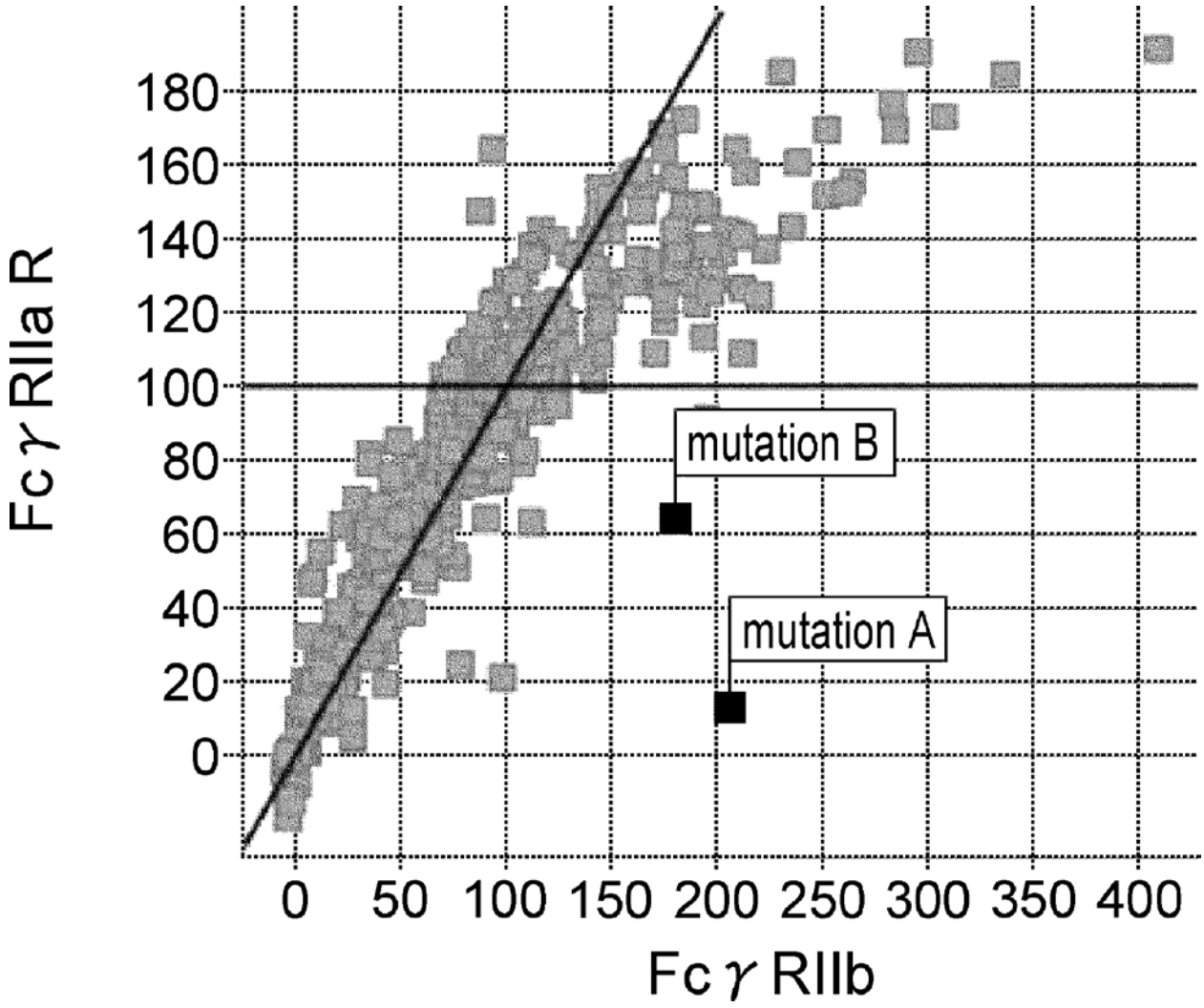

Fc γ RIIa R
180
160
140
120
100
80
60
40
20
0
mutation B
mutation A
0
50
100
150
200
250
300
350
400
Fc γ RIIb

FIG. 19

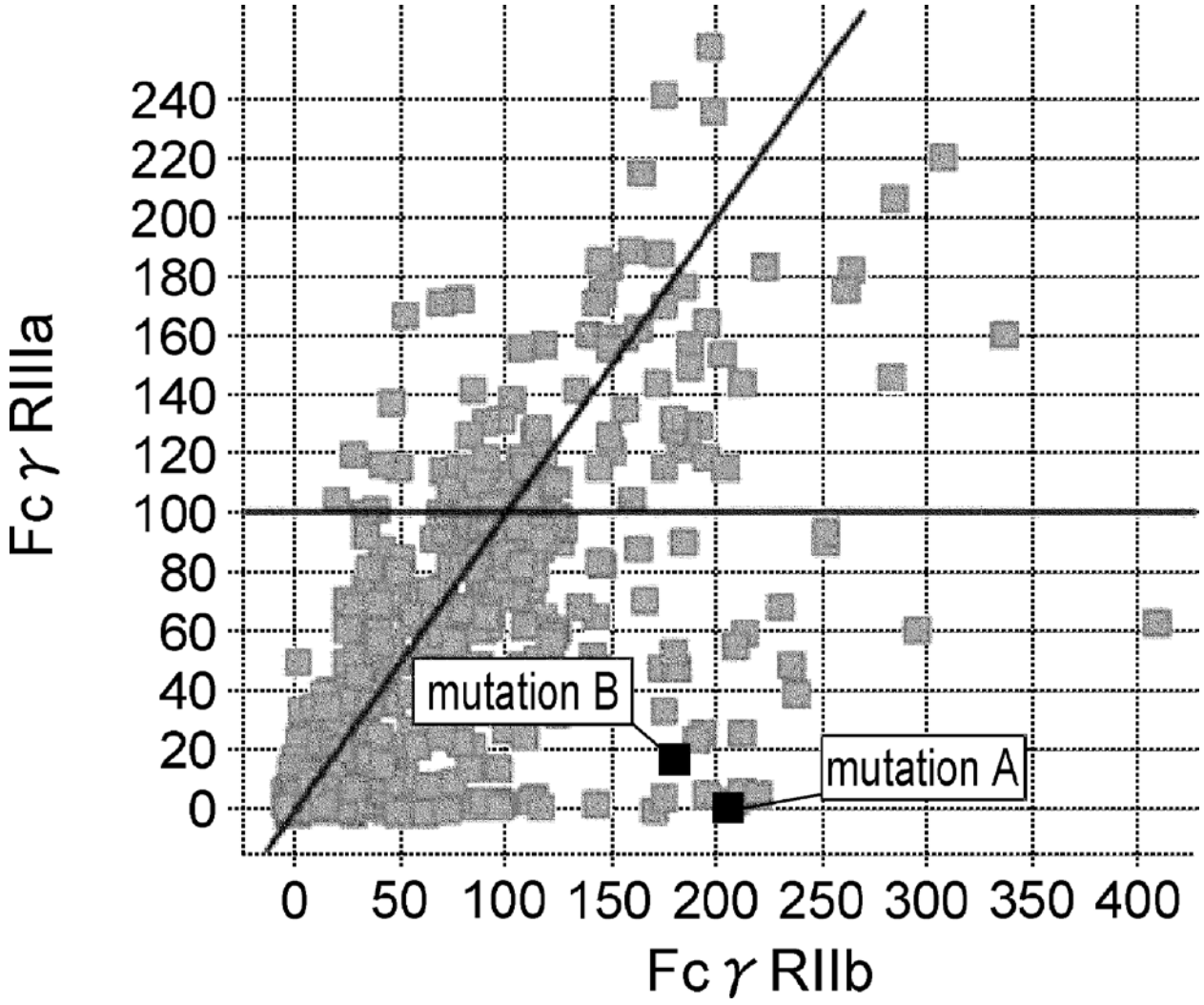

Fc γ RIIIa
240
220
200
180
160
140
120
100
80
60
40
20
0
0
50
100
150
200
250
300
350
400
Fc γ RIIb
mutation B
mutation A

FIG. 20

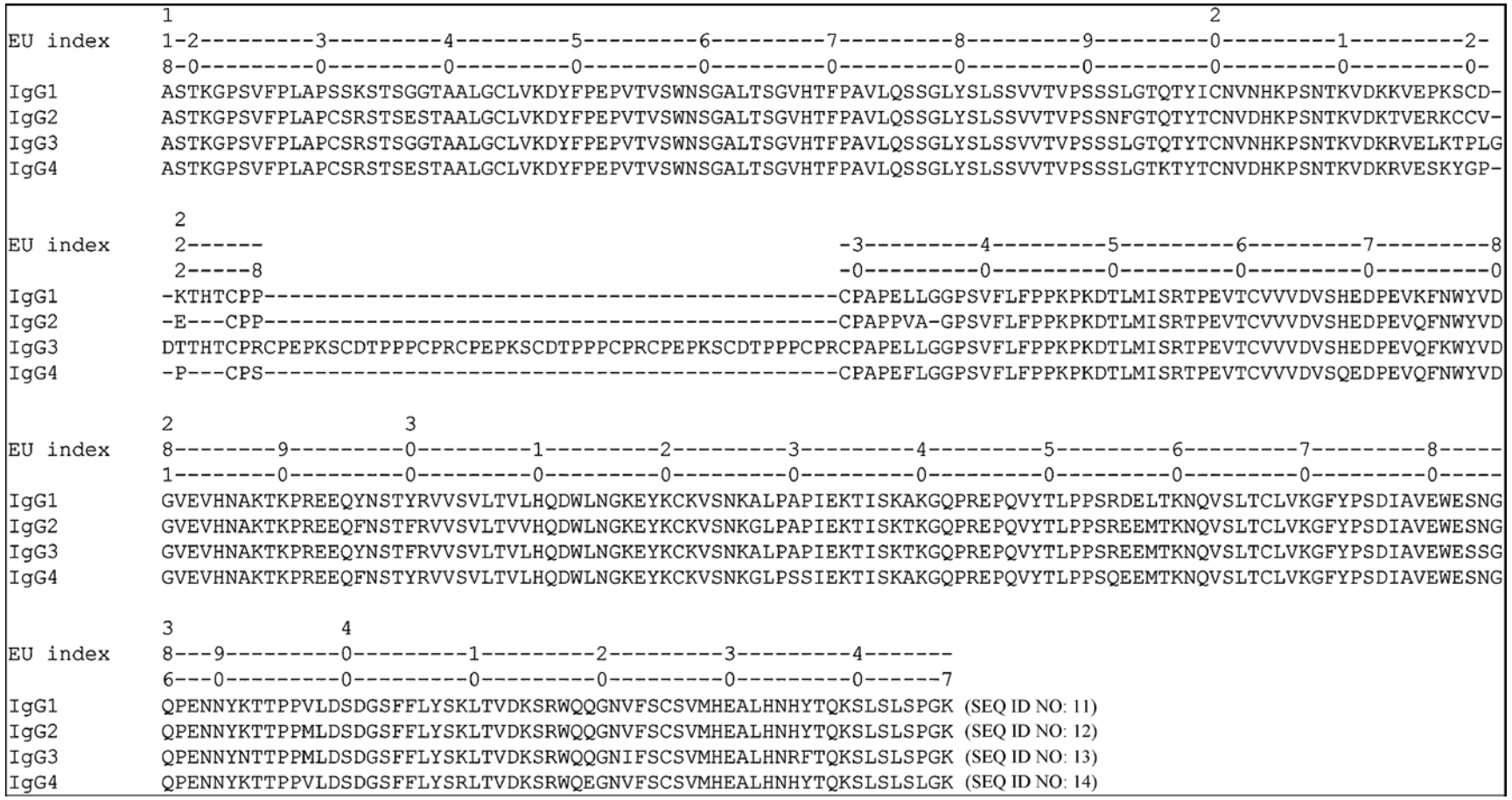

EU index
IgG1 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD-
IgG2 ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCV-
IgG3 ASTKGPSVFPLAPCSRSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVNHKPSNTKVDKRVELKTPLG
IgG4 ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGP-
EU index
IgG1 -KTHTCPP----------CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
IgG2 -E---CPP----------CPAPPVA-GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVD
IgG3 DTTHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFKWYVD
IgG4 -P---CPS----------CPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD
EU index
IgG1 GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNG
IgG2 GVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG
IgG3 GVEVHNAKTKPREEQYNSTFRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESSG
IgG4 GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNG
EU index
IgG1 QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 11)
IgG2 QPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 12)
IgG3 QPENNYNTTPPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK (SEQ ID NO: 13)
IgG4 QPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 14)

FIG. 21

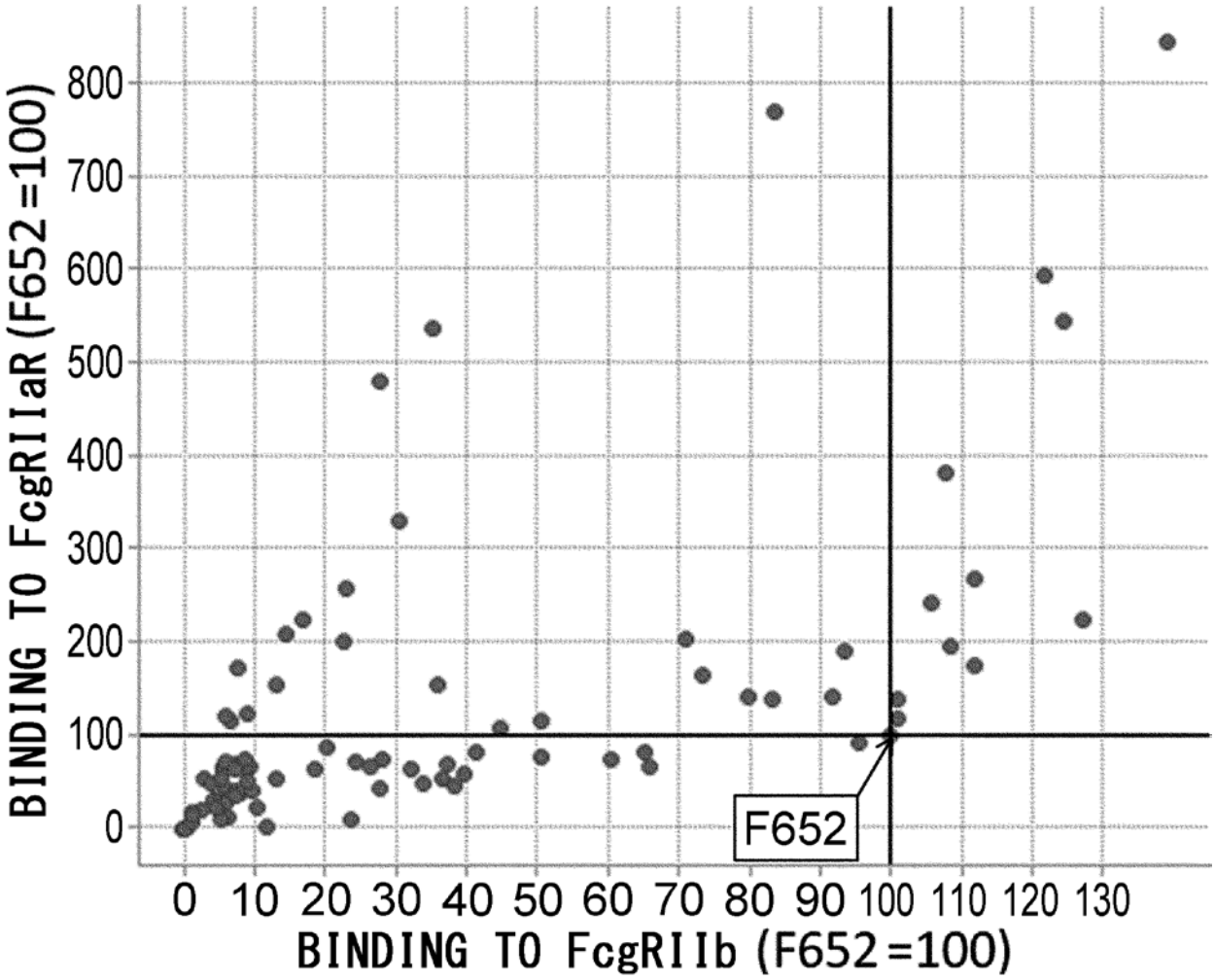

BINDING TO FcgRIIaR (F652=100)
800
700
600
500
400
300
200
100
0
F652
0 10 20 30 40 50 60 70 80 90 100 110 120 130
BINDING TO FcgRIIb (F652=100)

FIG. 22

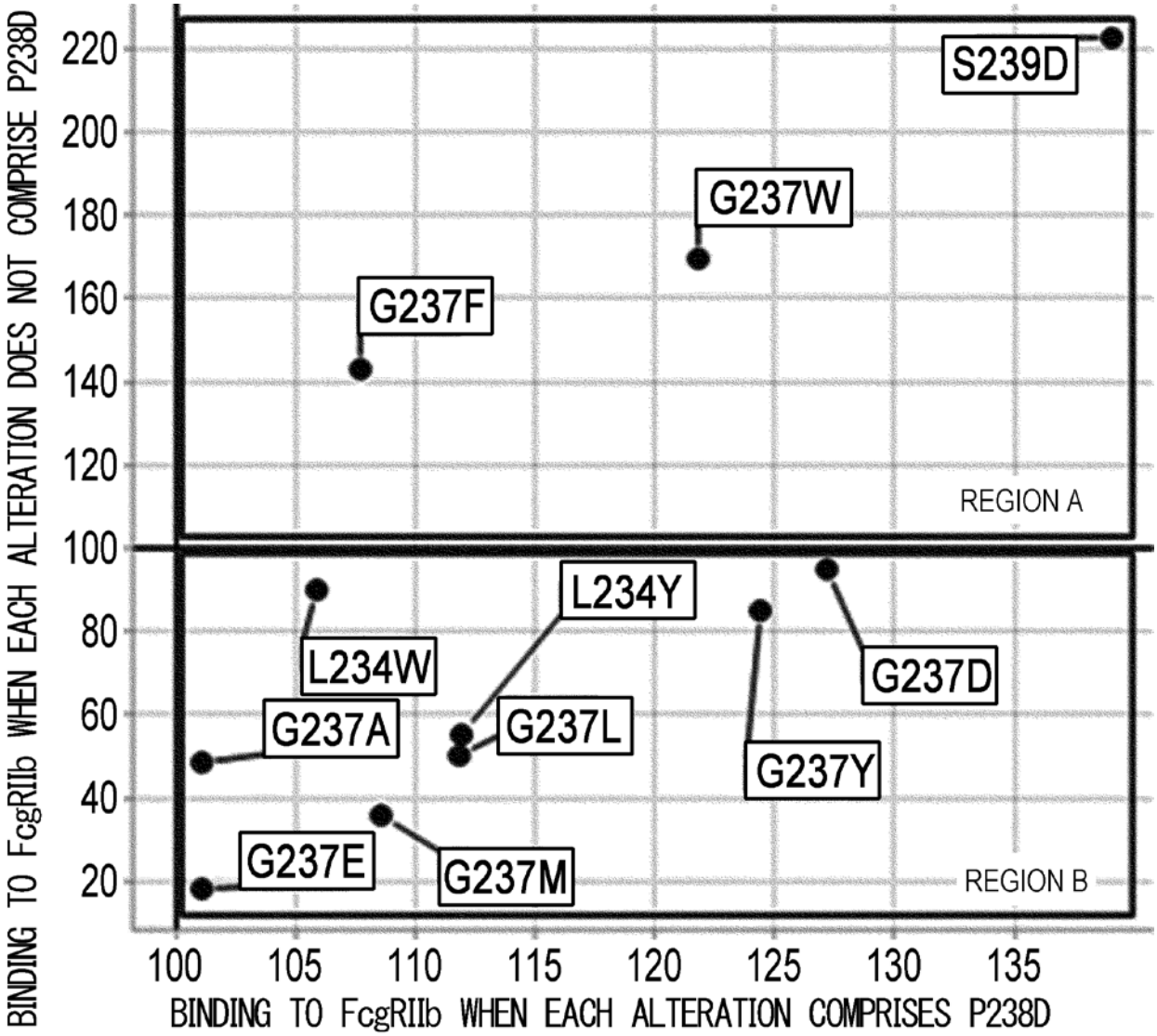

BINDING TO FcgRIIb WHEN EACH ALTERATION DOES NOT COMPRISE P238D
220
200
180
160
140
120
100
80
60
40
20
S239D
G237W
G237F
REGION A
L234Y
L234W
G237D
G237A
G237L
G237Y
G237E
G237M
REGION B
100
105
110
115
120
125
130
135
BINDING TO FcgRIIb WHEN EACH ALTERATION COMPRISES P238D

FIG. 23

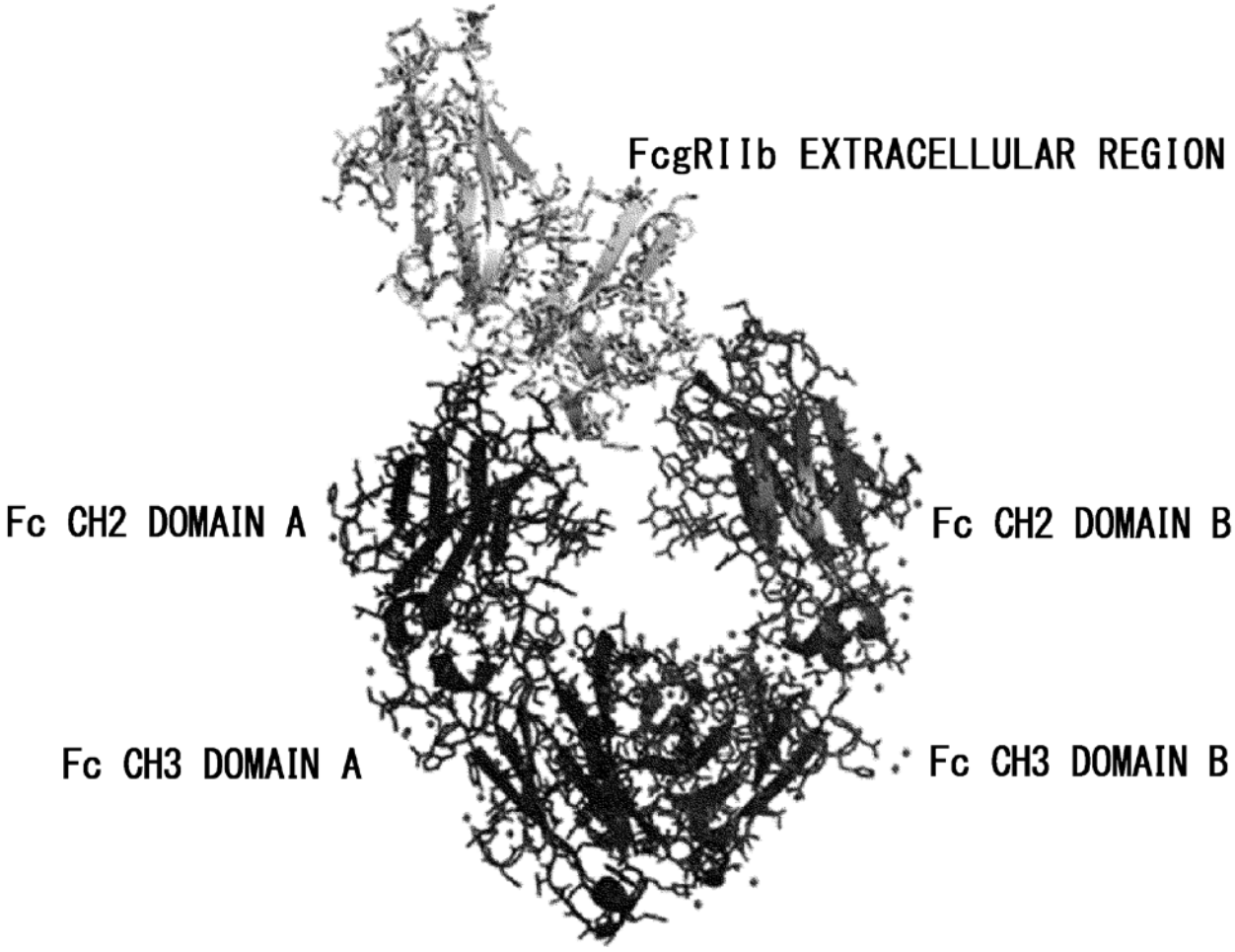
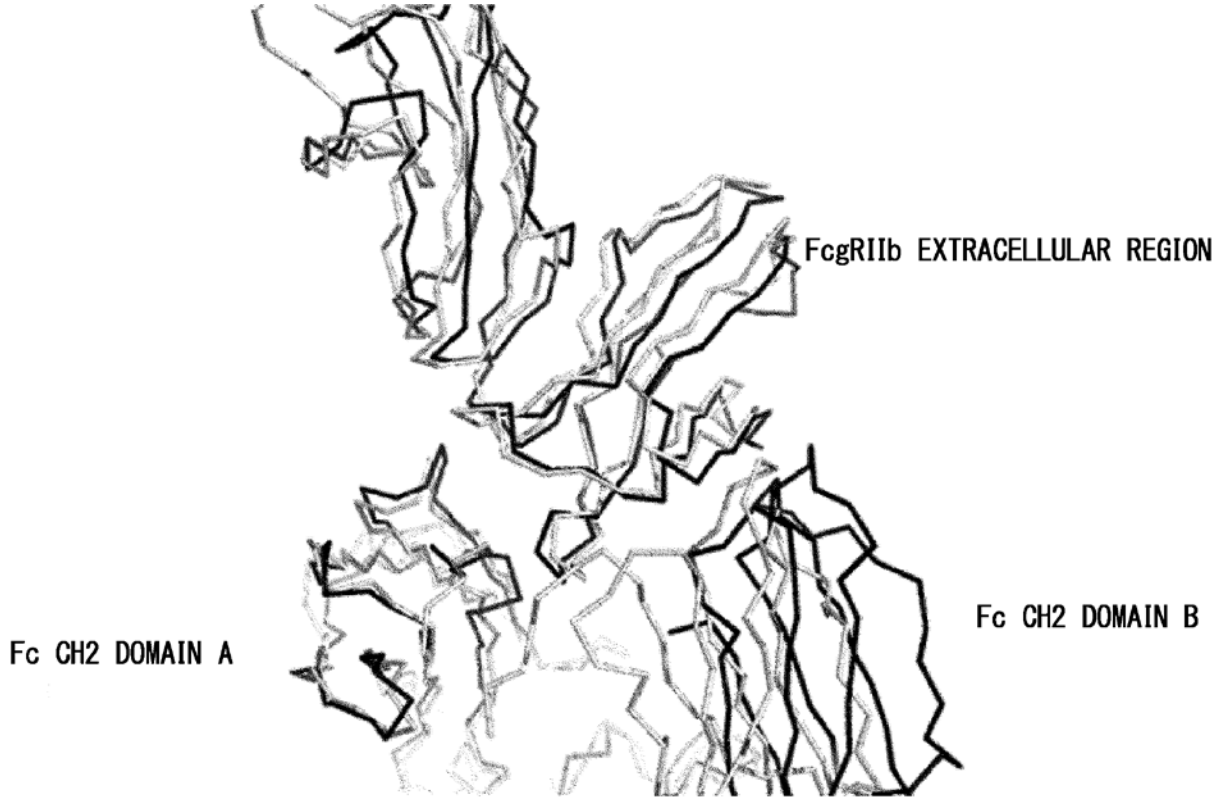
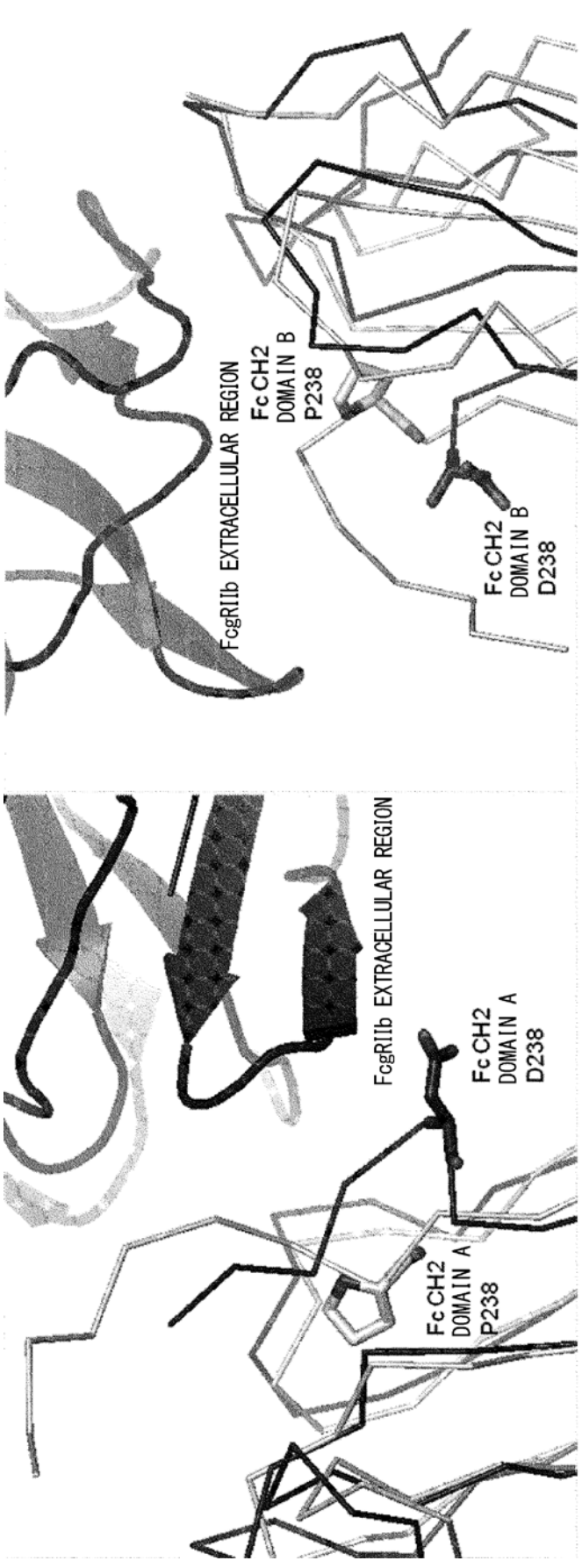

FcgRIIb EXTRACELLULAR REGION
Fc CH2 DOMAIN A
Fc CH2 DOMAIN B
Fc CH3 DOMAIN A
Fc CH3 DOMAIN B

FIG. 24



BLACK CRYSTAL STRUCTURE OF Fc(P238D)/Fcγ RIIb EXTRACELLULAR REGION COMPLEX
GRAY MODEL STRUCTURE OF Fc(WT)/Fcγ RIIb EXTRACELLULAR REGION COMPLEX

FIG. 25



BLACK CRYSTAL STRUCTURE OF Fc(P238D)/Fcγ RIIb EXTRACELLULAR REGION COMPLEX
GRAY MODEL STRUCTURE OF Fc(WT)/Fcγ RIIb EXTRACELLULAR REGION COMPLEX

FIG. 26

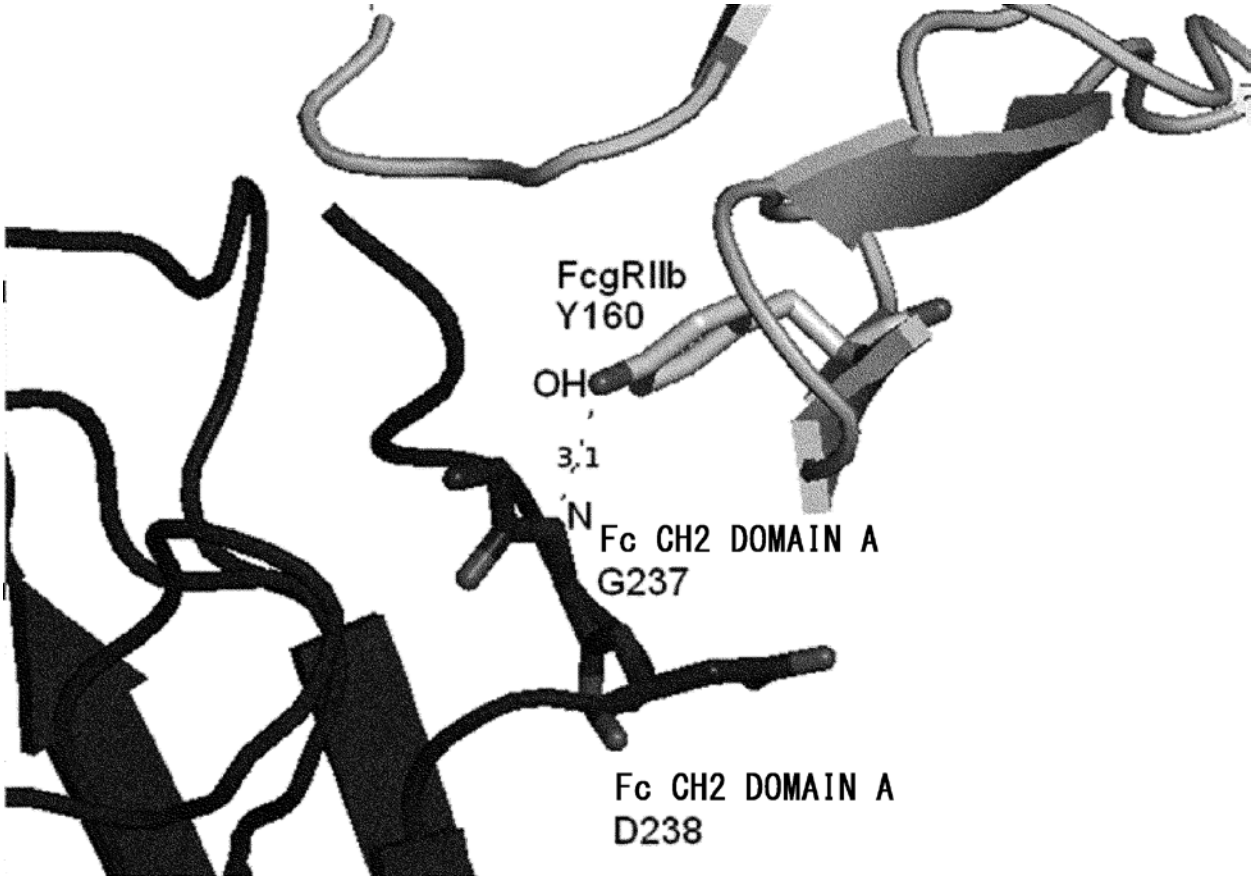


FIG. 27

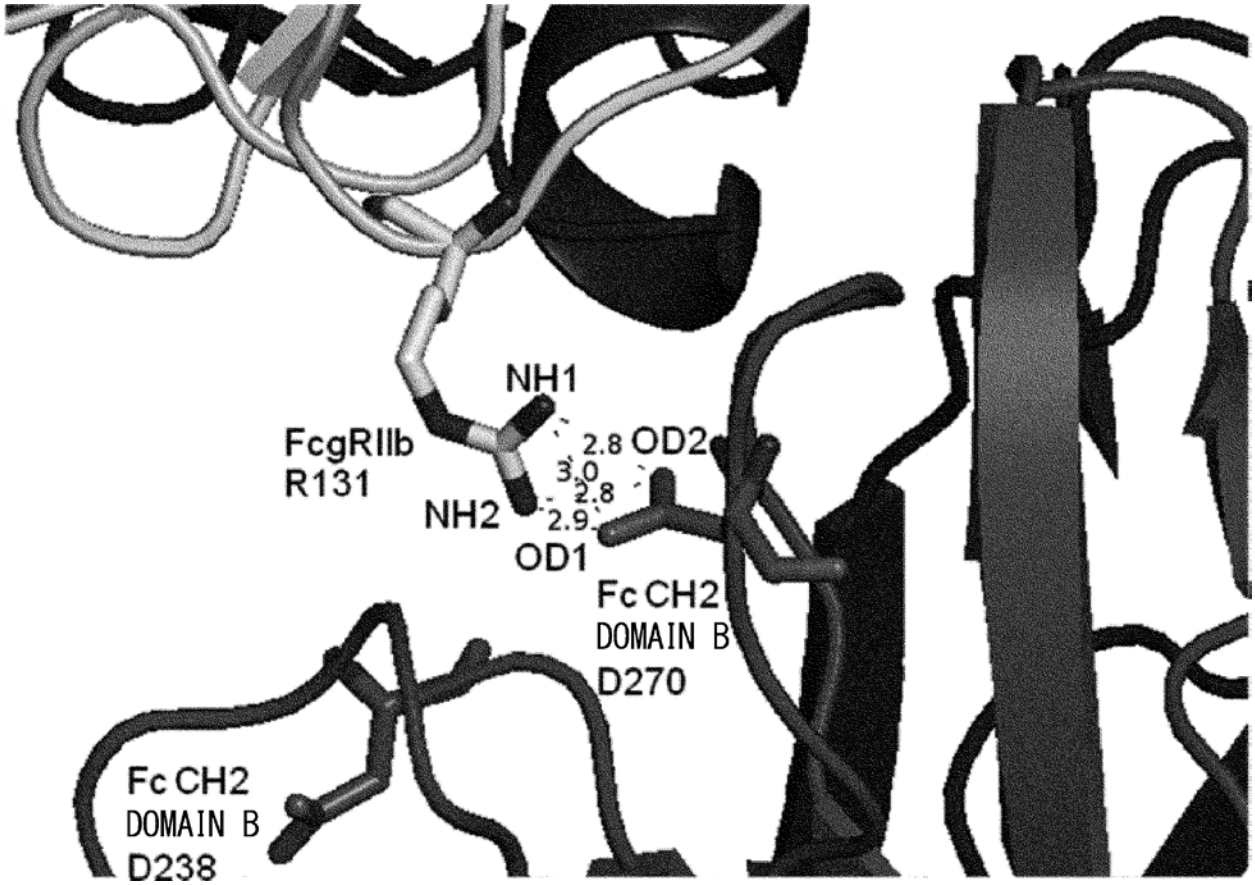

NH1
FcgRIIb
R131
2.8
OD2
3.0
2.8
NH2
2.9
OD1
Fc CH2
DOMAIN B
D270
Fc CH2
DOMAIN B
D238

FIG. 28

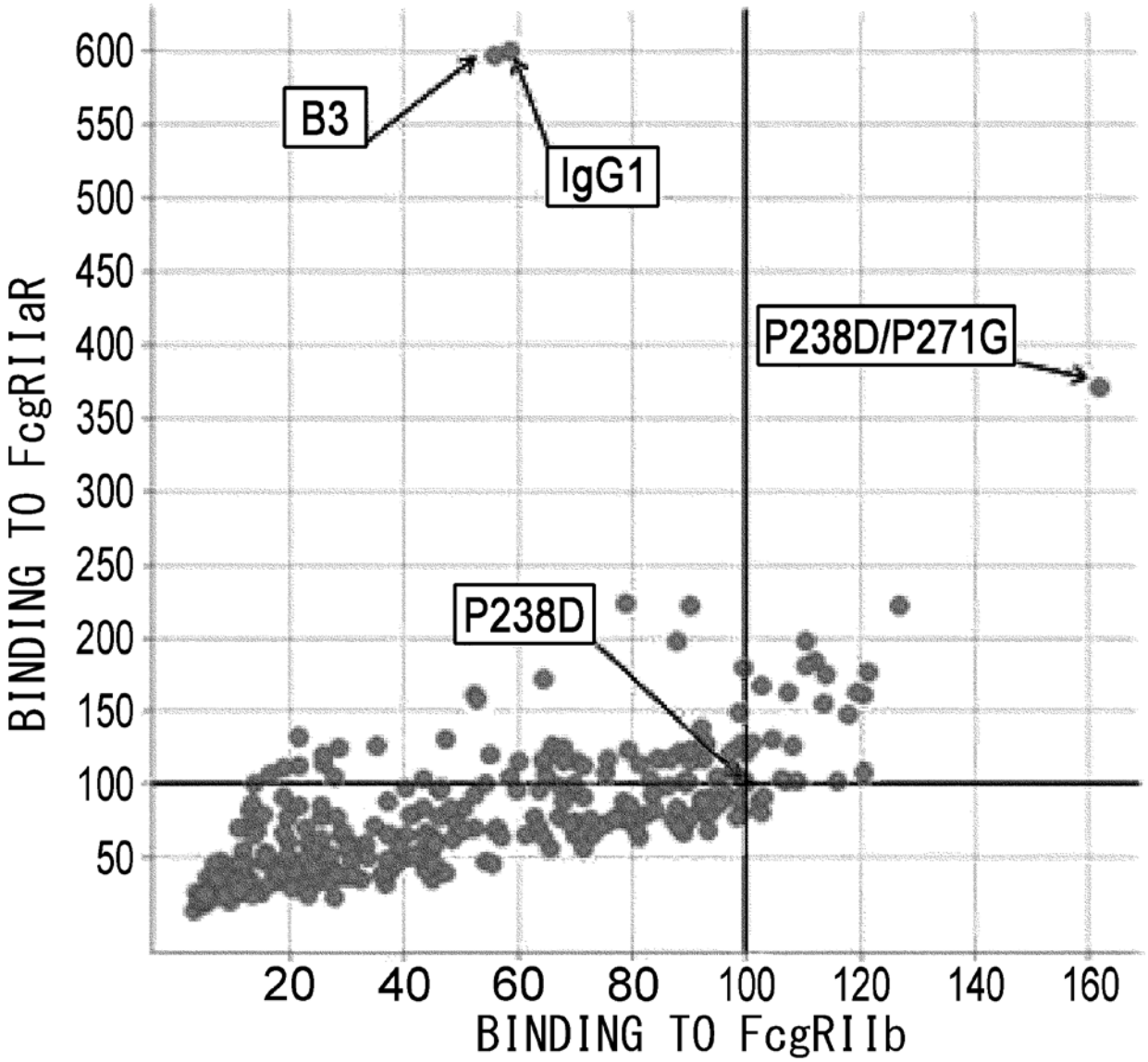

B3
IgG1
P238D/P271G
P238D
BINDING TO FcgRIIaR
BINDING TO FcgRIIb
600
550
500
450
400
350
300
250
200
150
100
50
20
40
60
80
100
120
140
160

FIG. 29

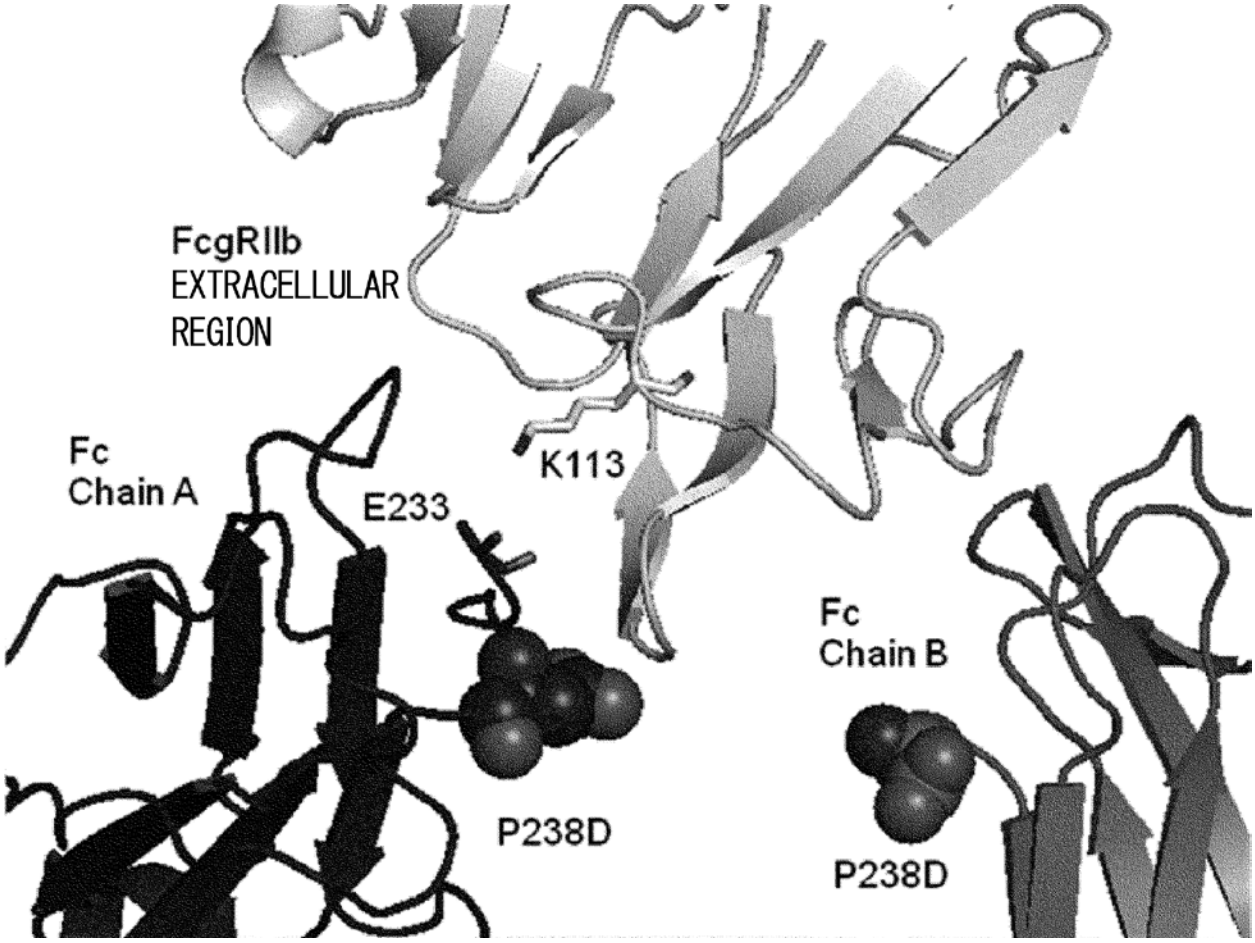

FcgRIIb
EXTRACELLULAR
REGION
Fc
Chain A
E233
K113
Fc
Chain B
P238D
P238D

FIG. 30

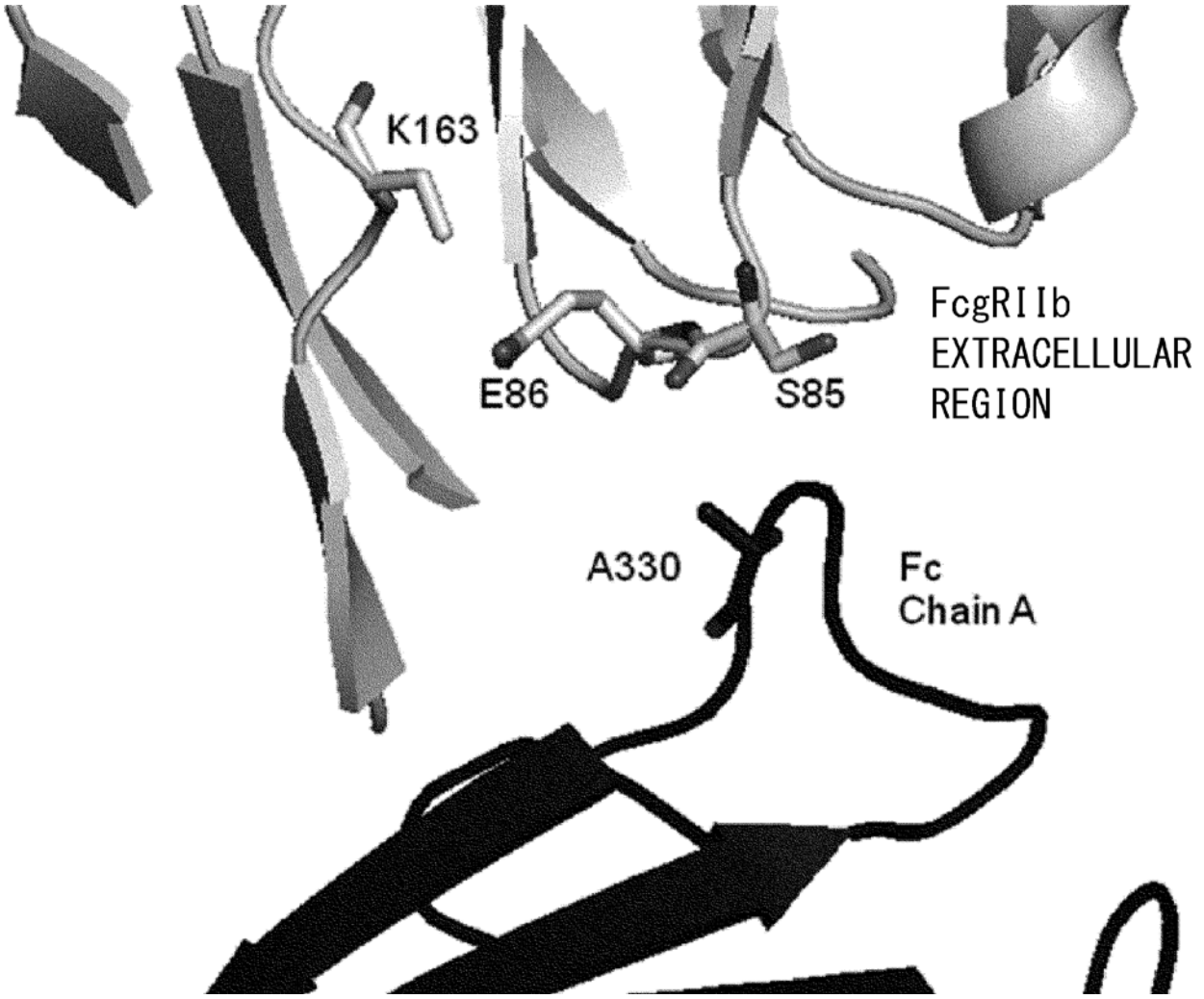
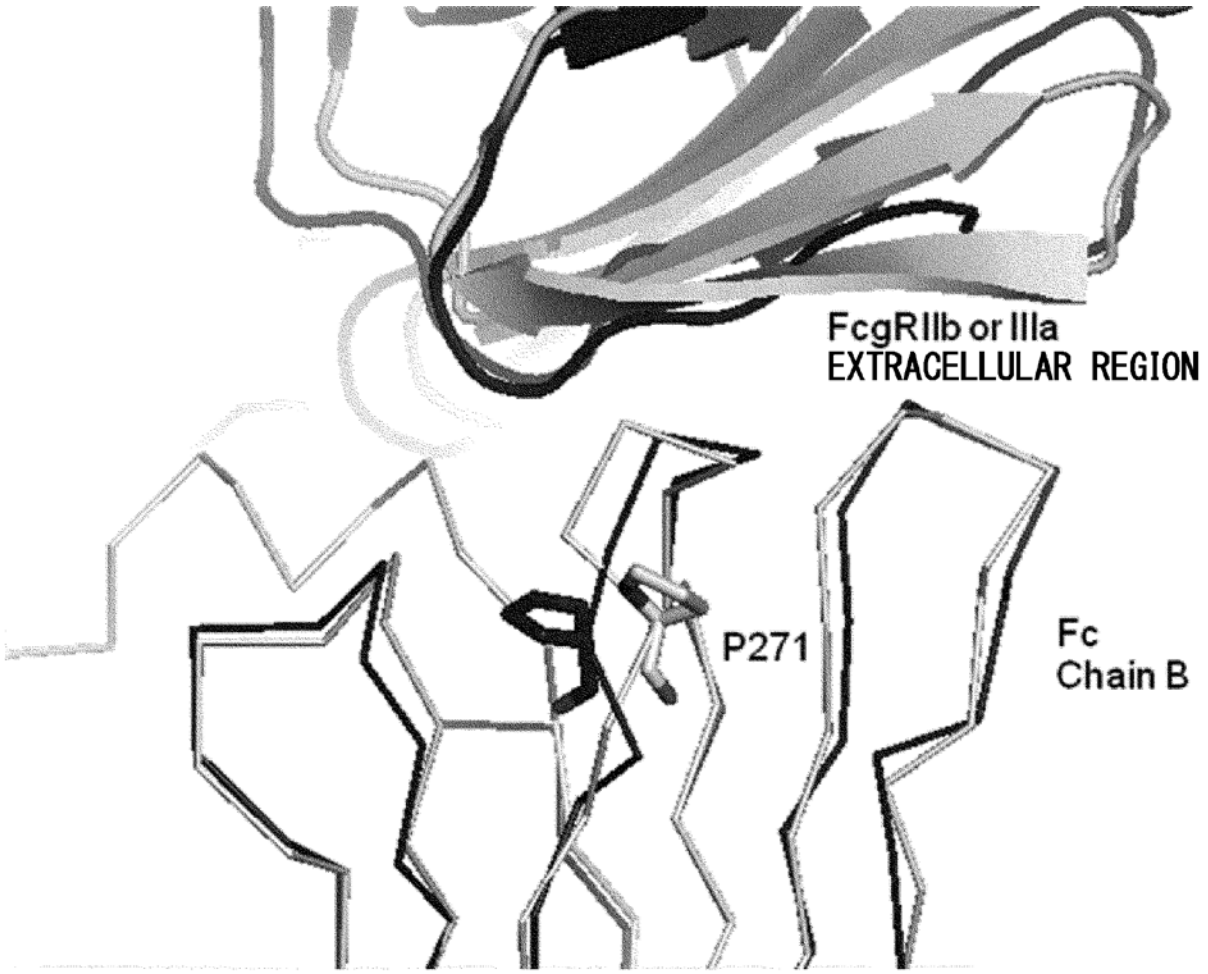


FIG. 31



BLACK CRYSTAL STRUCTURE OF Fc(P238D)/FcγRIIb EXTRACELLULAR REGION COMPLEX
GRAY CRYSTAL STRUCTURE OF Fc(WT)/FcγRIIIa EXTRACELLULAR REGION COMPLEX (PDB code: 3SGJ)

FIG. 32

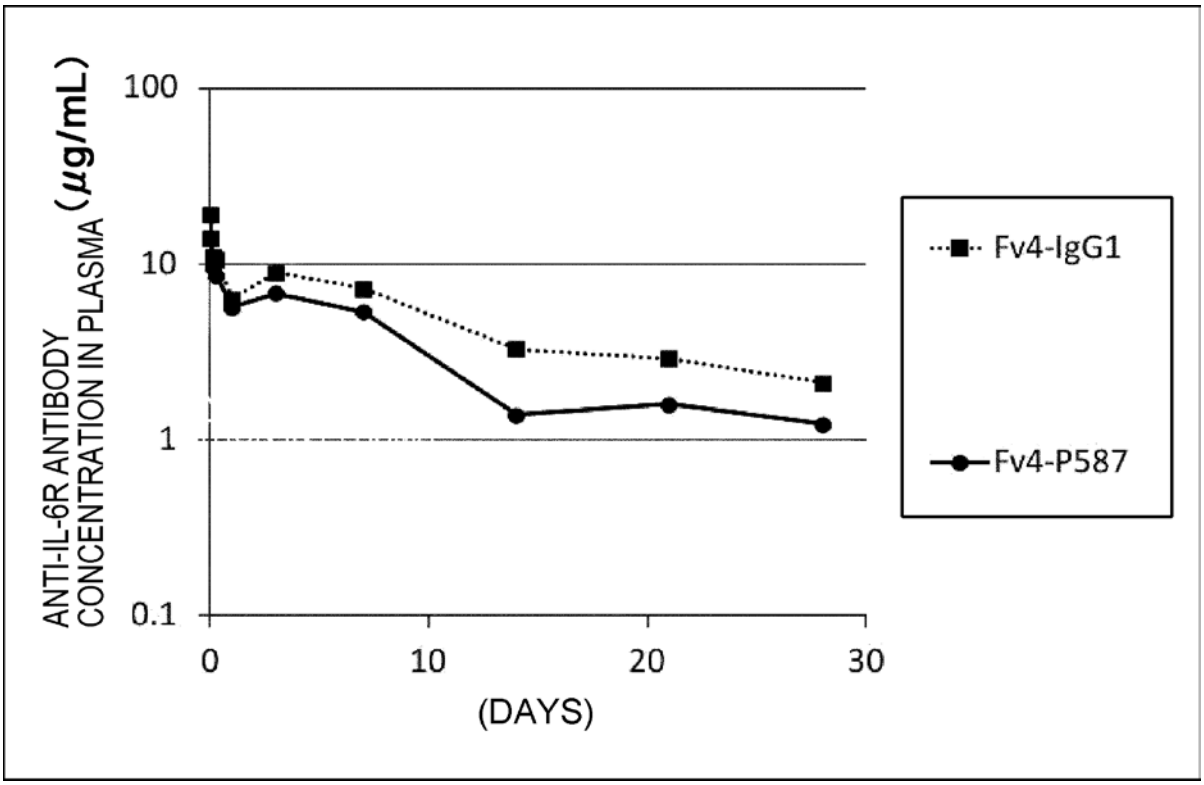

ANTI-IL-6R ANTIBODY CONCENTRATION IN PLASMA (μg/mL)
100
10
1
0.1
0
10
20
30
(DAYS)
Fv4-IgG1
Fv4-P587

FIG. 33

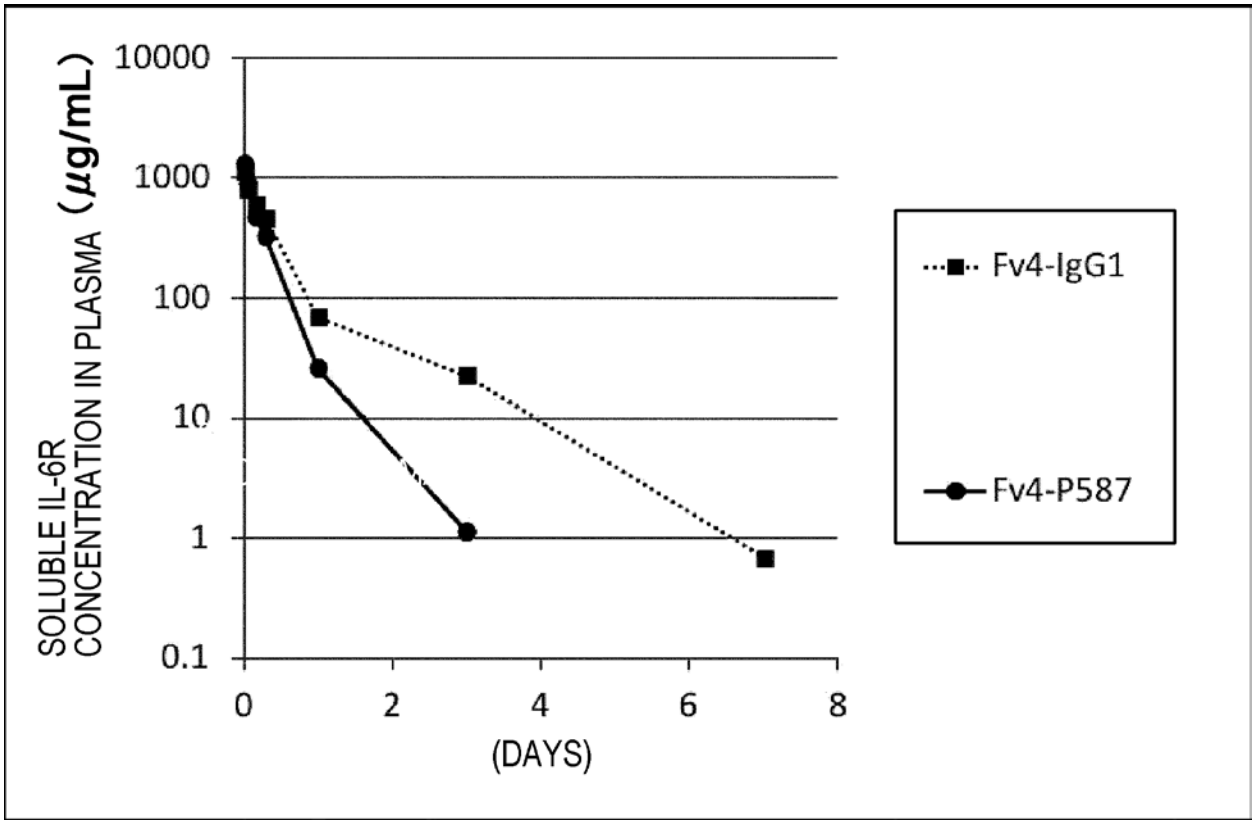

SOLUBLE IL-6R CONCENTRATION IN PLASMA (μg/mL)
10000
1000
100
10
1
0.1
0
2
4
6
8
(DAYS)
Fv4-IgG1
Fv4-P587

FIG. 34

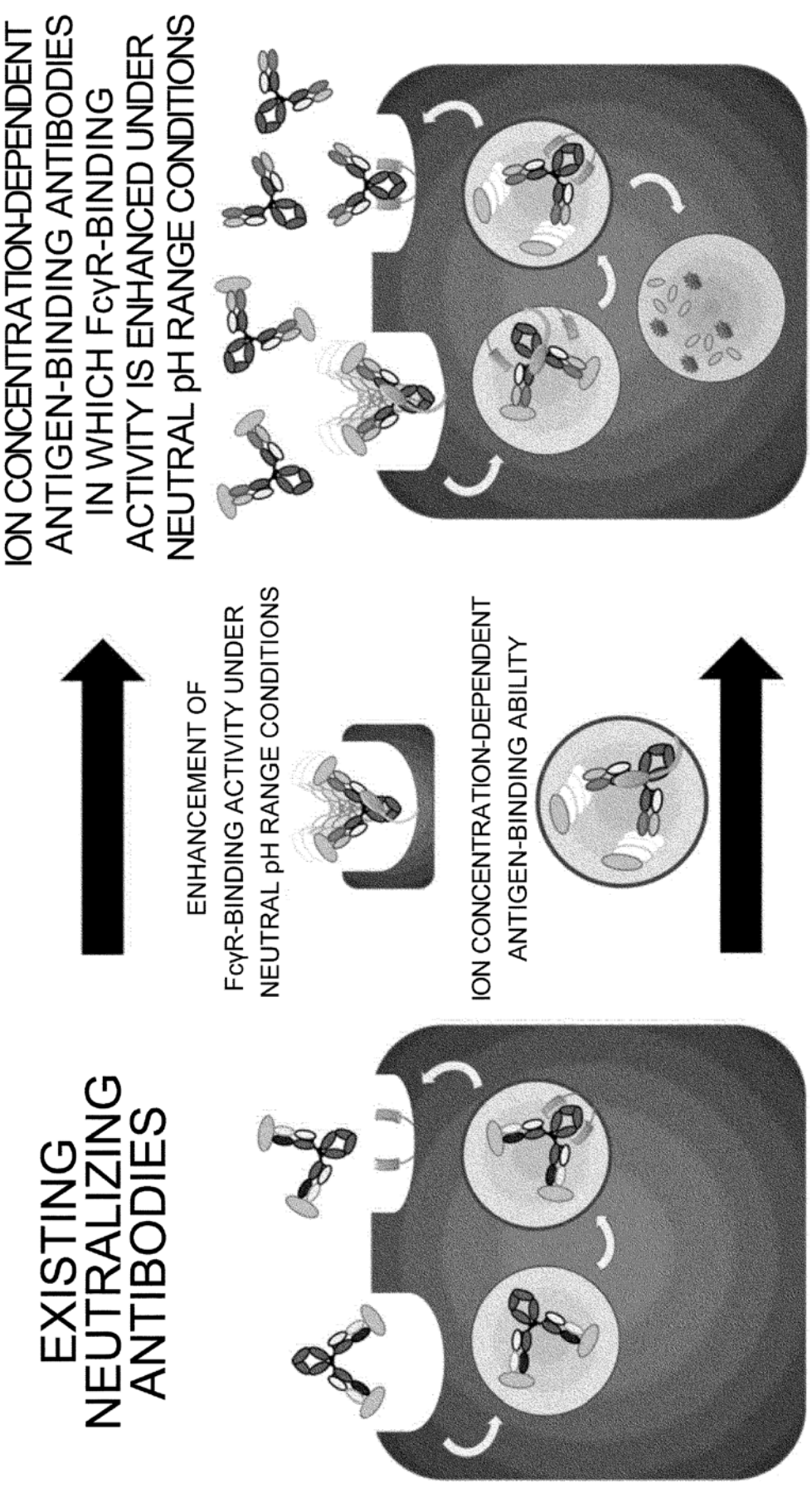

EXISTING NEUTRALIZING ANTIBODIES
ENHANCEMENT OF FcγR-BINDING ACTIVITY UNDER NEUTRAL pH RANGE CONDITIONS
ION CONCENTRATION-DEPENDENT ANTIGEN-BINDING ABILITY
ION CONCENTRATION-DEPENDENT ANTIGEN-BINDING ANTIBODIES IN WHICH FcγR-BINDING ACTIVITY IS ENHANCED UNDER NEUTRAL pH RANGE CONDITIONS

FIG. 35

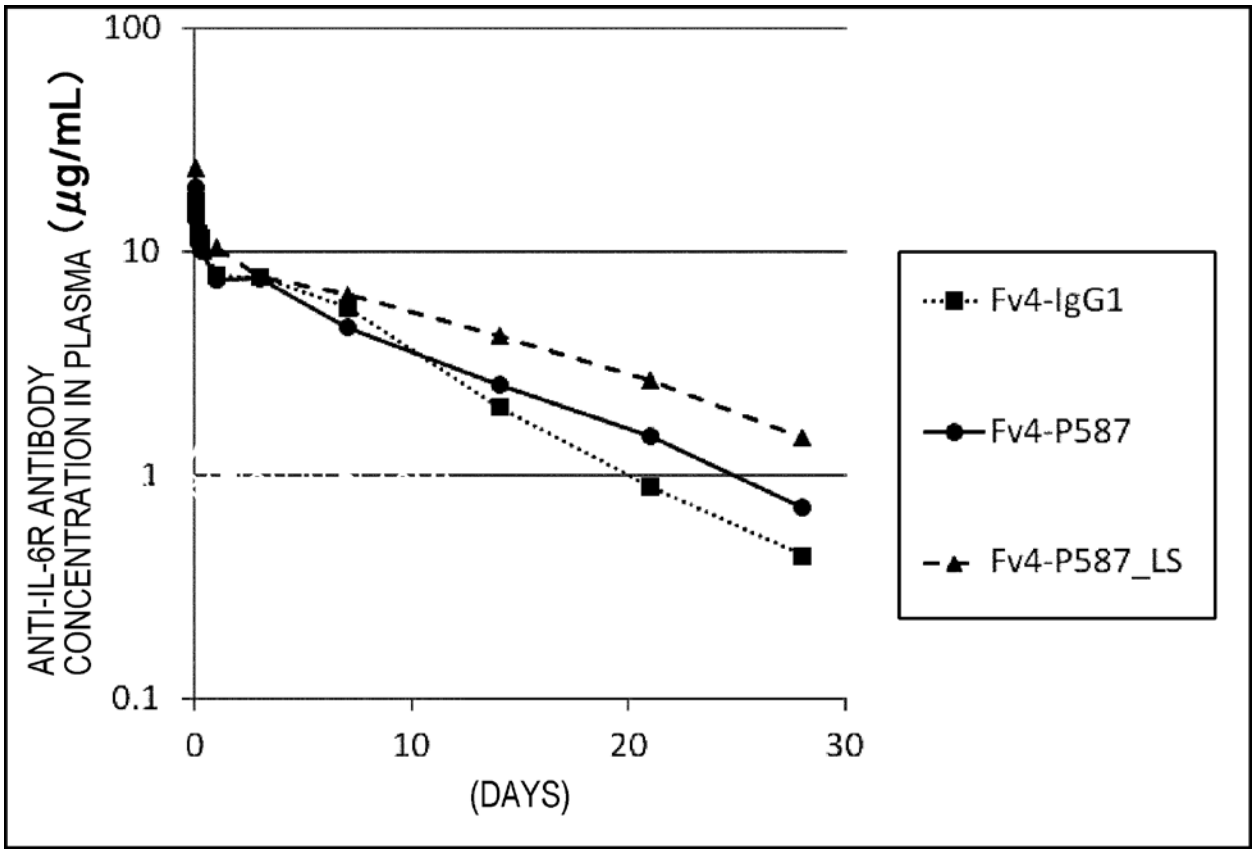

100
10
1
0.1
ANTI-IL-6R ANTIBODY CONCENTRATION IN PLASMA (μg/mL)
0
10
20
30
(DAYS)
Fv4-IgG1
Fv4-P587
Fv4-P587_LS

FIG. 36

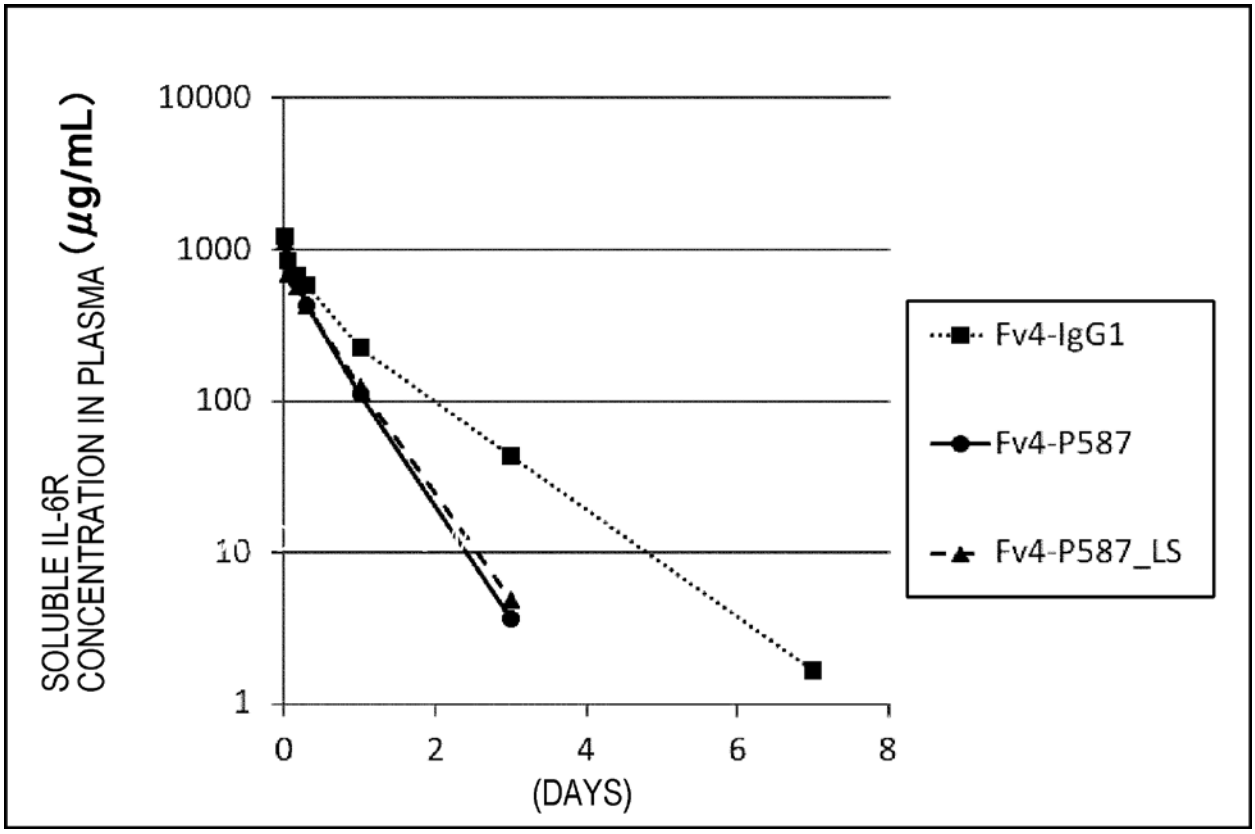

SOLUBLE IL-6R CONCENTRATION IN PLASMA (μg/mL)
10000
1000
100
10
1
0
2
4
6
8
(DAYS)
Fv4-IgG1
Fv4-P587
Fv4-P587_LS

FIG. 37