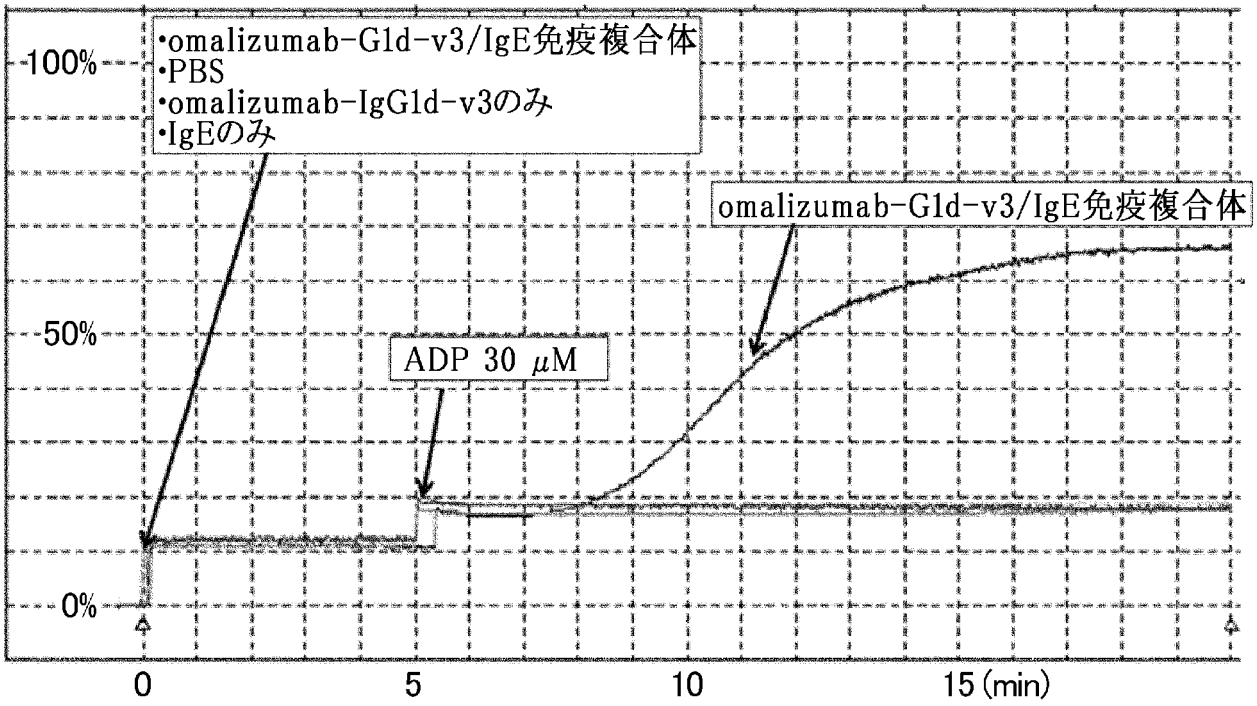
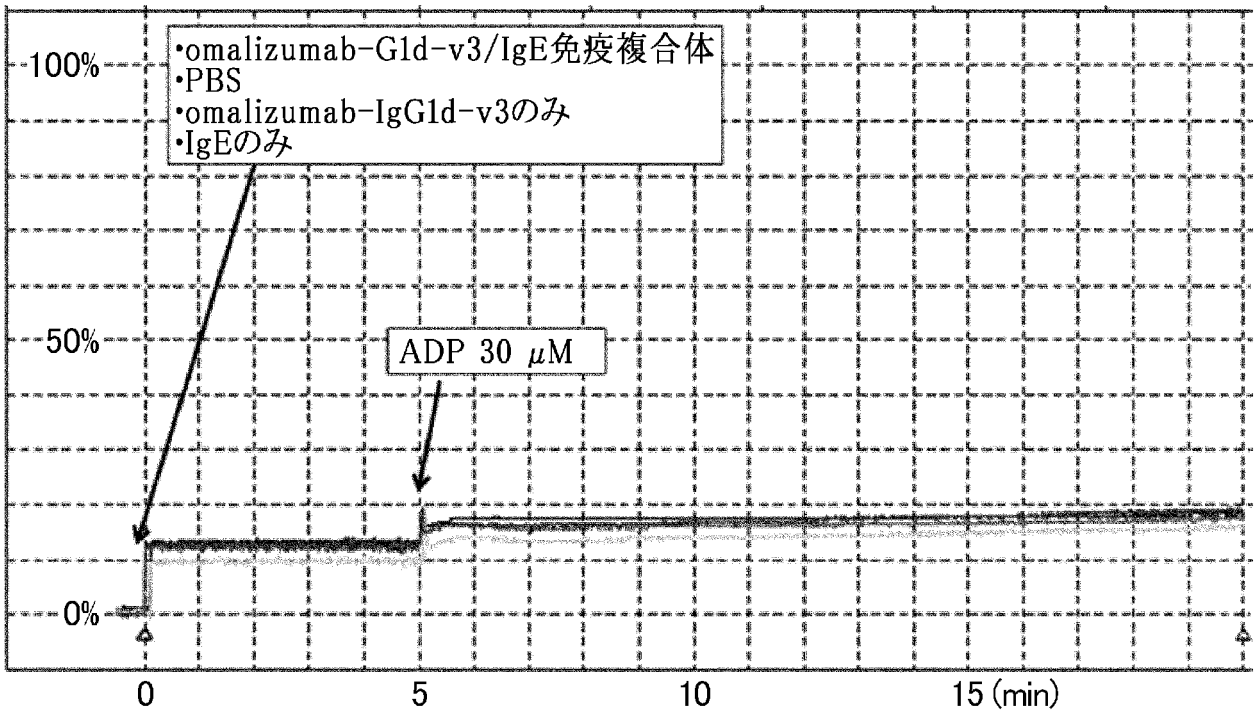
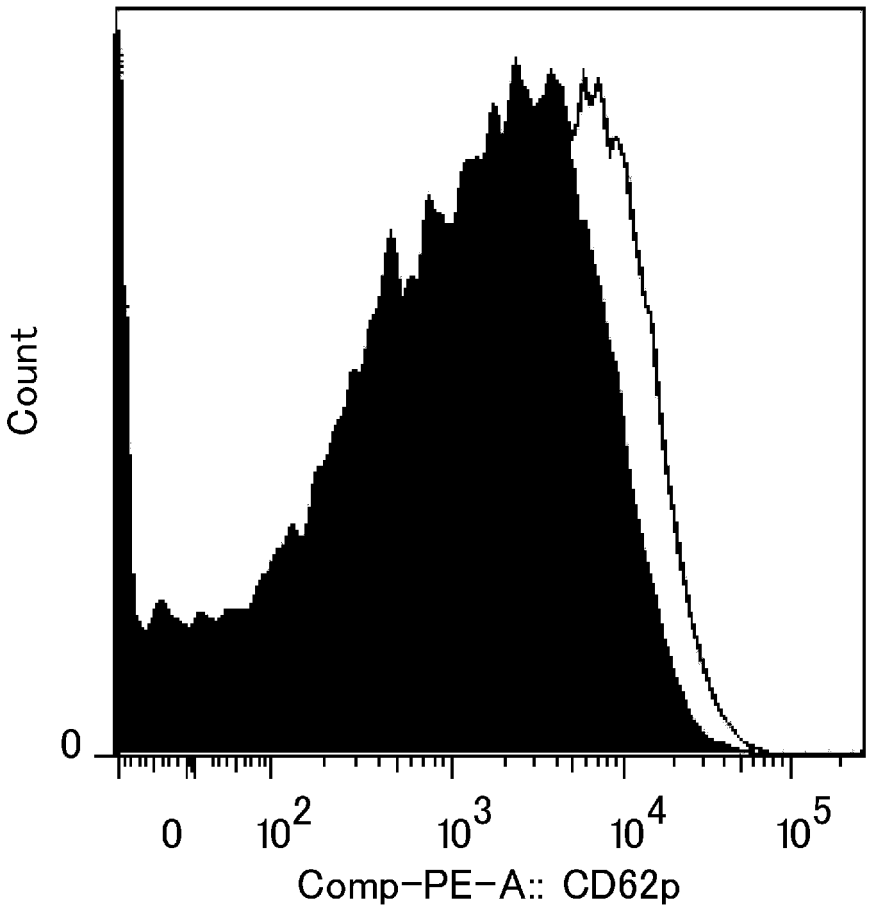
[図1]


•omalizumab-G1d-v3/IgE免疫複合体
•PBS
•omalizumab-IgG1d-v3のみ
•IgEのみ
100%
50%
0%
ADP 30 μM
omalizumab-G1d-v3/IgE免疫複合体
0
5
10
15 (min)

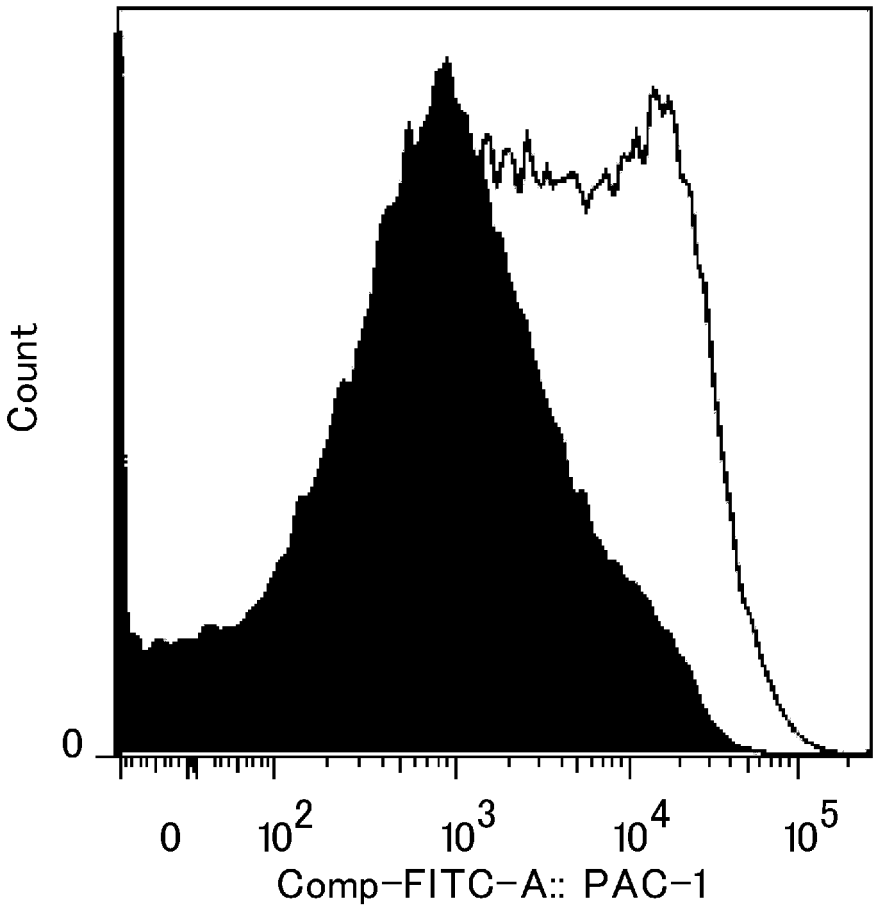
[図2]


•omalizumab-G1d-v3/IgE免疫複合体
•PBS
•omalizumab-IgG1d-v3のみ
•IgEのみ
100%
50%
0%
ADP 30 μM
0
5
10
15 (min)

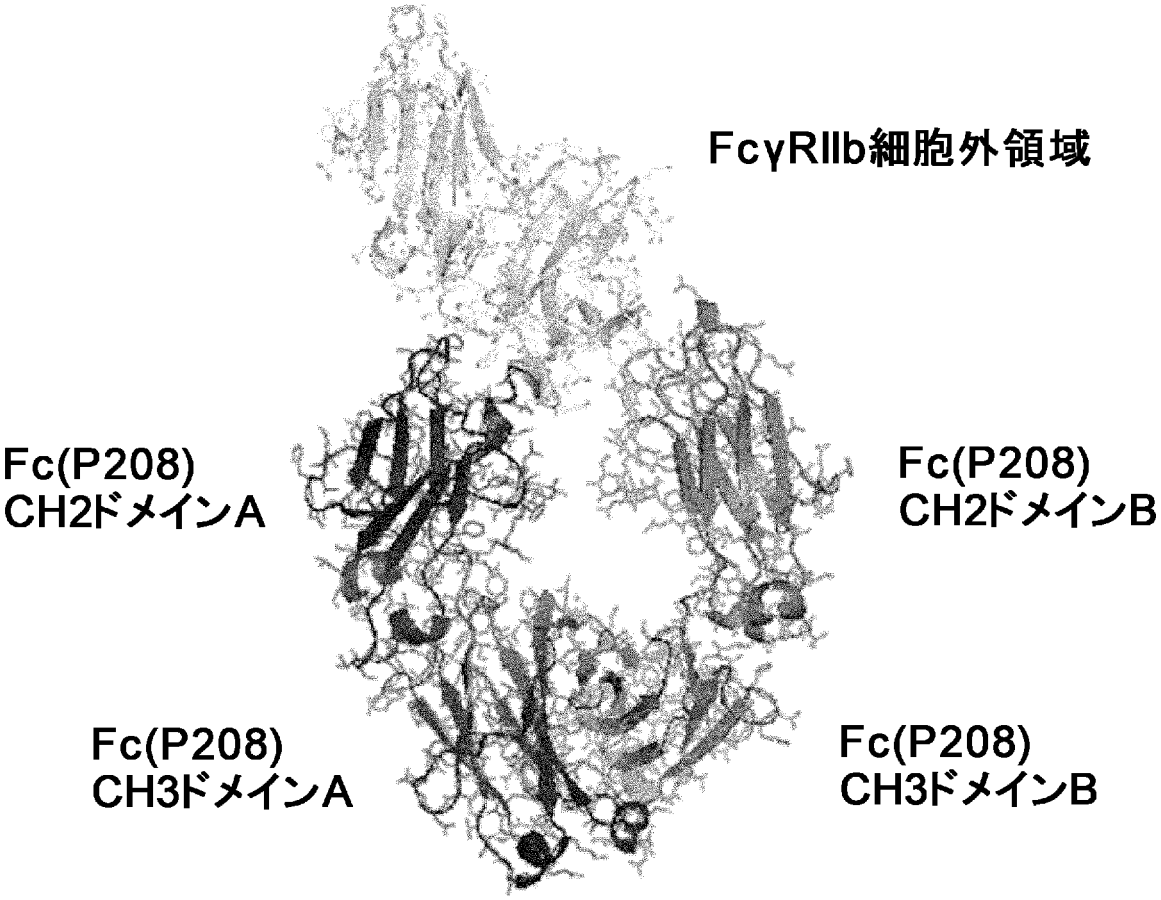
[図3]


Count
0
0
10^2
10^3
10^4
10^5
Comp-PE-A:: CD62p

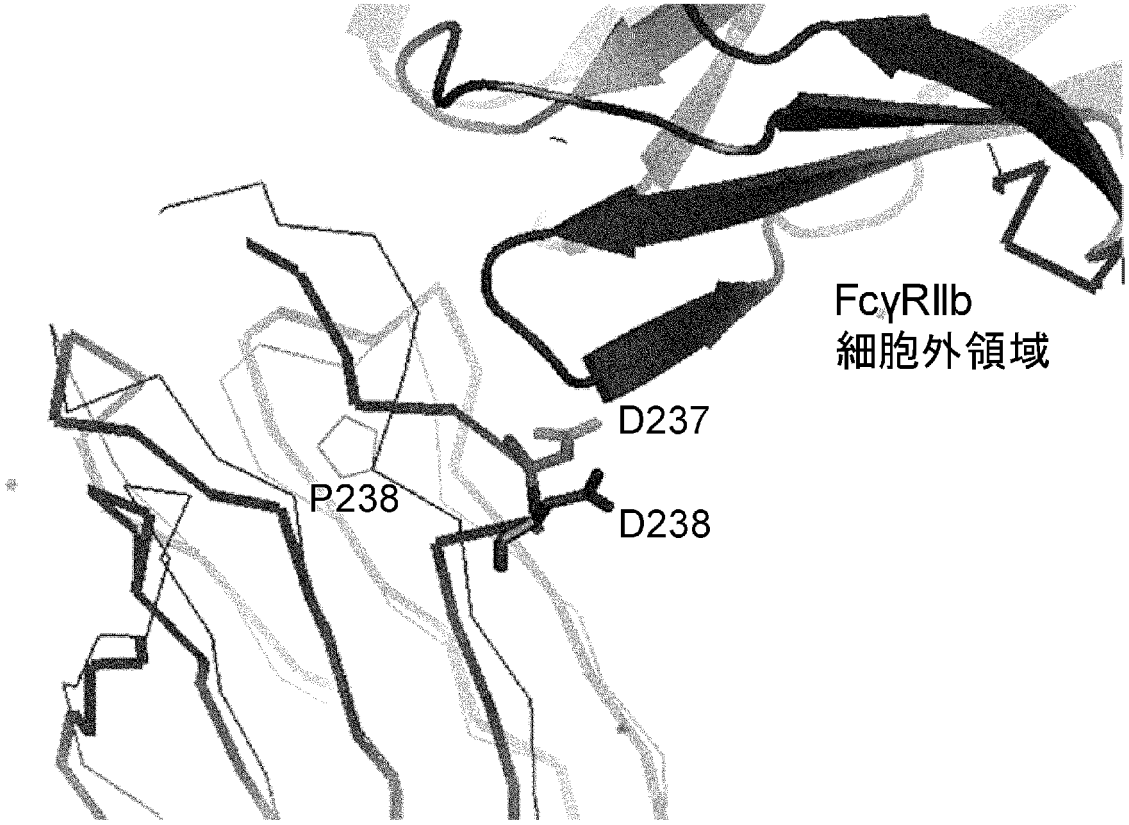
[図4]


Count
0
0
10^2
10^3
10^4
10^5
Comp-FITC-A:: PAC-1

[図5]

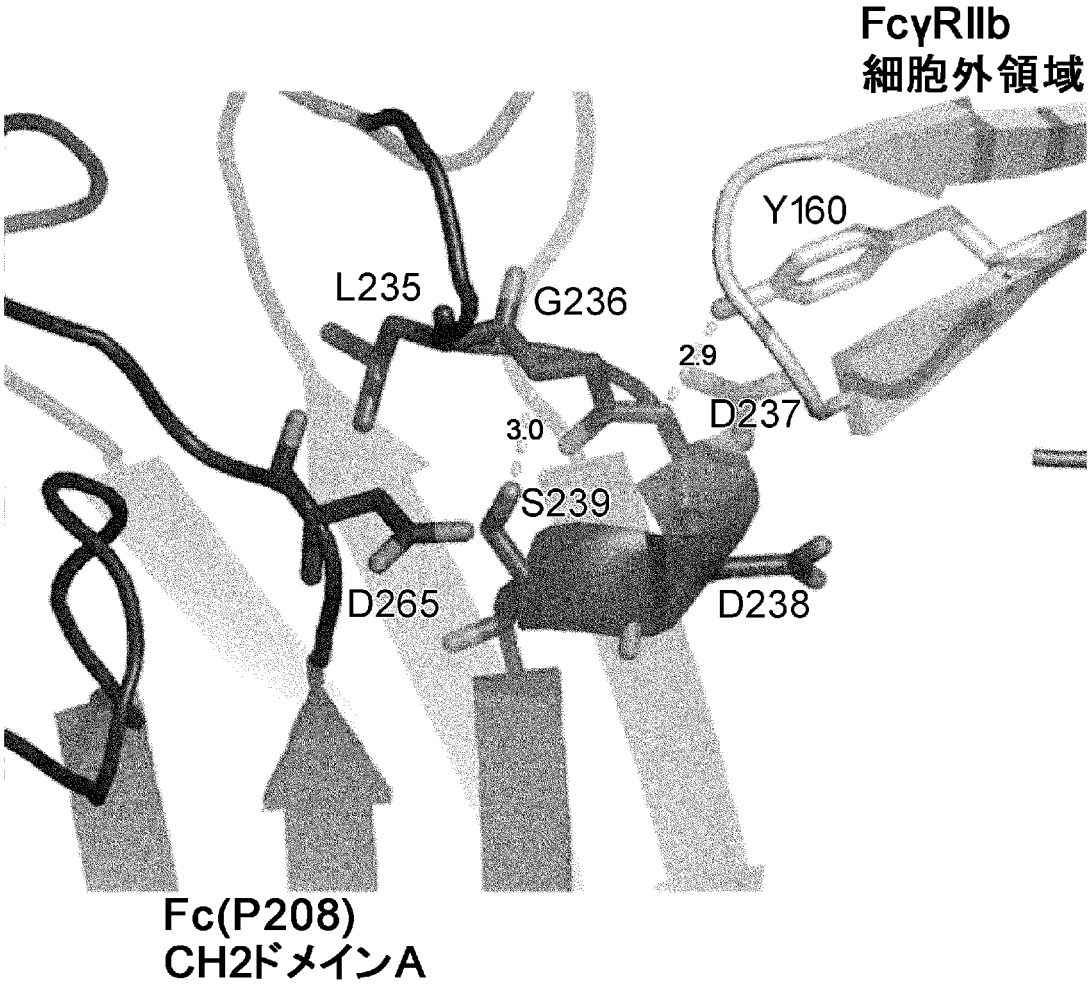


[図6]

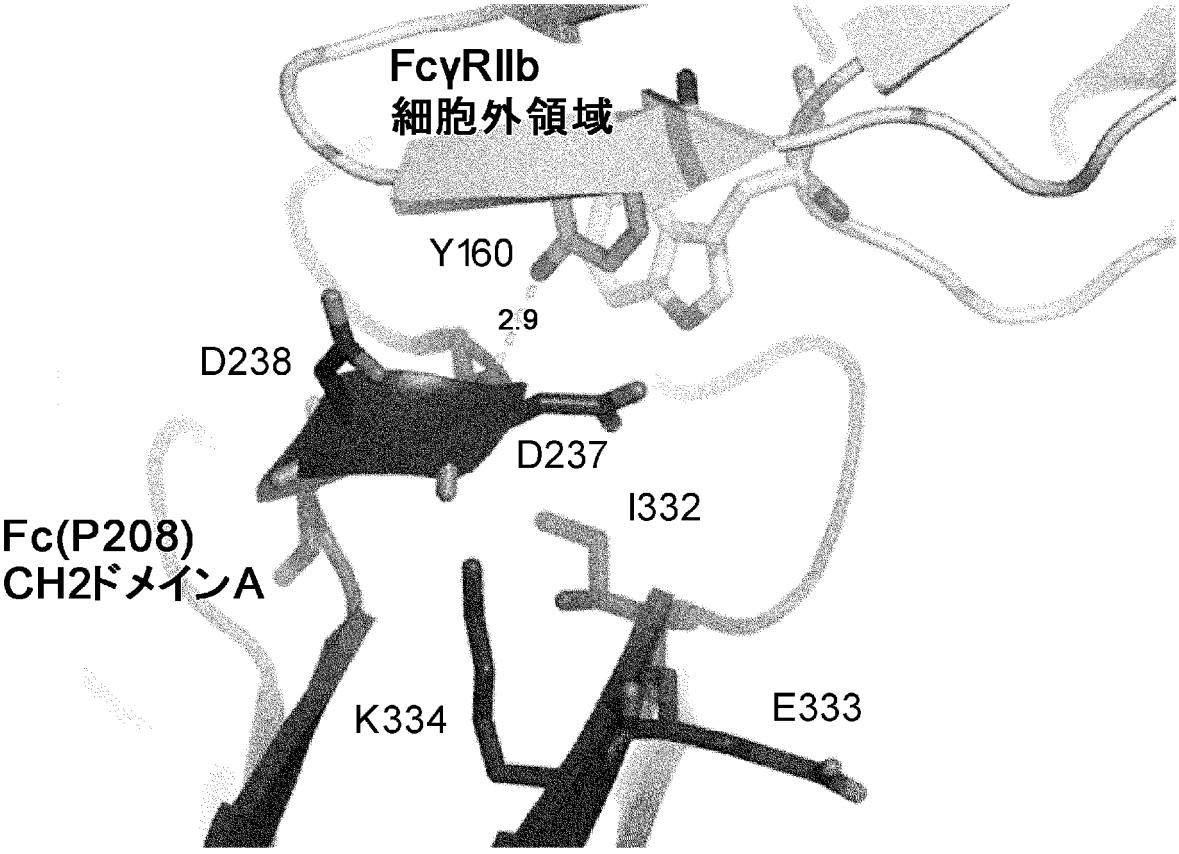


細線: Fc(Wt)CH2ドメインA
太線: Fc(P208)CH2ドメインA

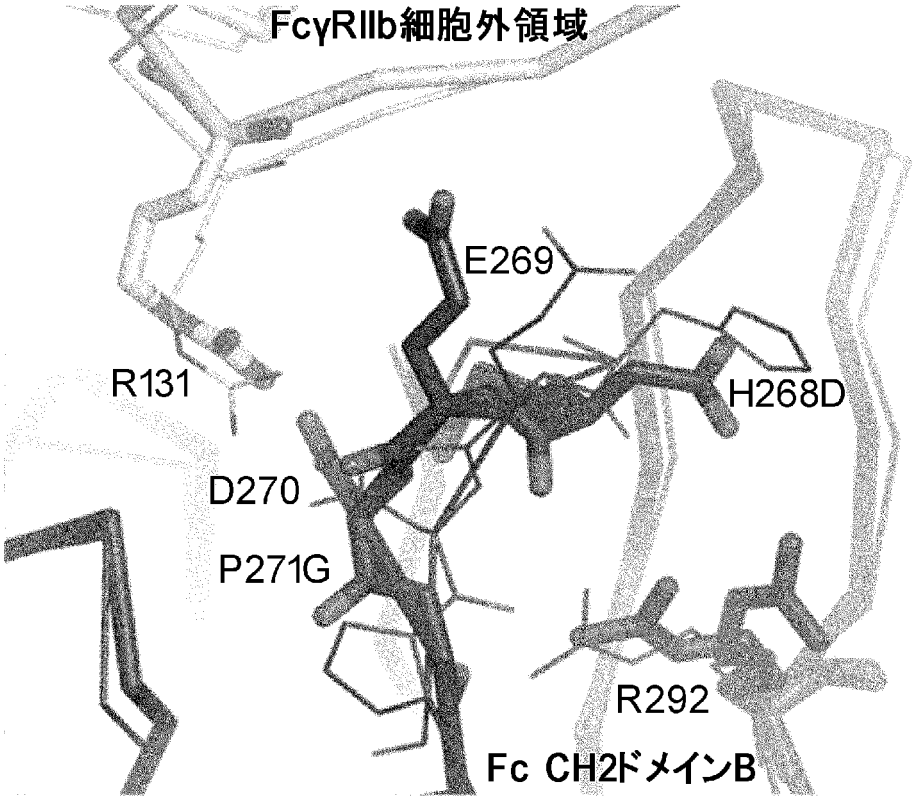
[図7]


FcγRIIb
細胞外領域
Y160
L235
G236
2.9
D237
3.0
S239
D265
D238
Fc(P208)
CH2ドメインA

[図8]

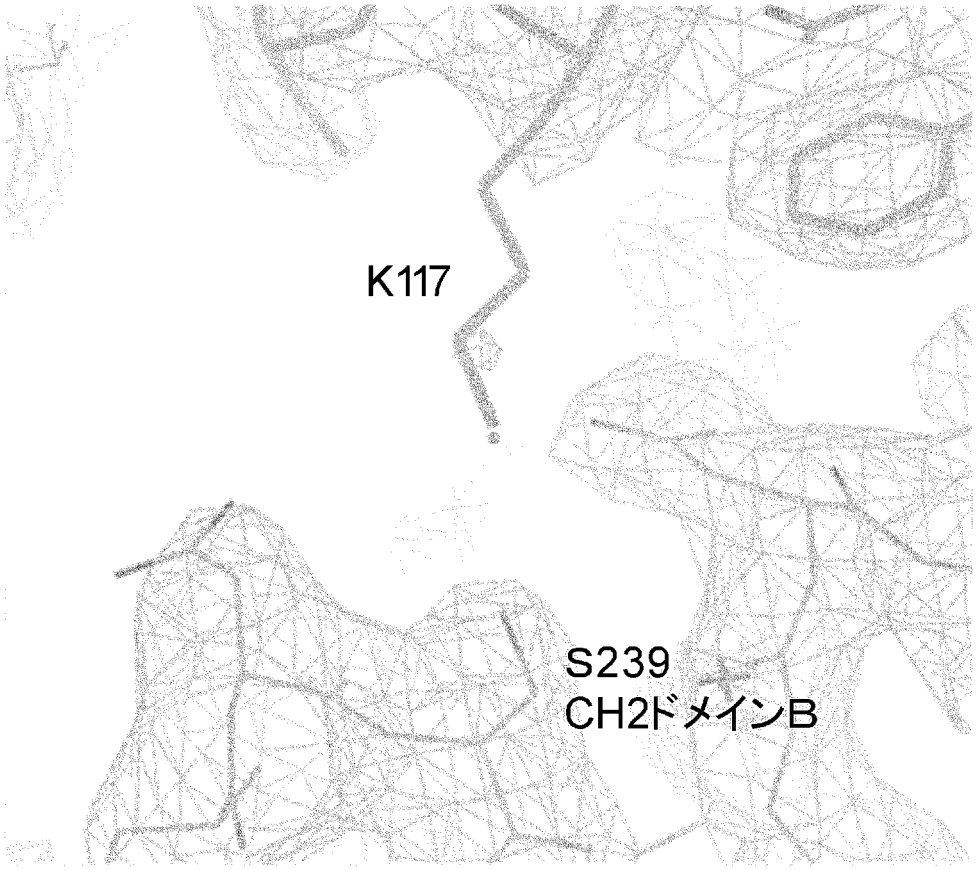

FcγRIIb
細胞外領域
Y160
2.9
D238
D237
I332
Fc(P208)
CH2ドメインA
K334
E333

[図9]



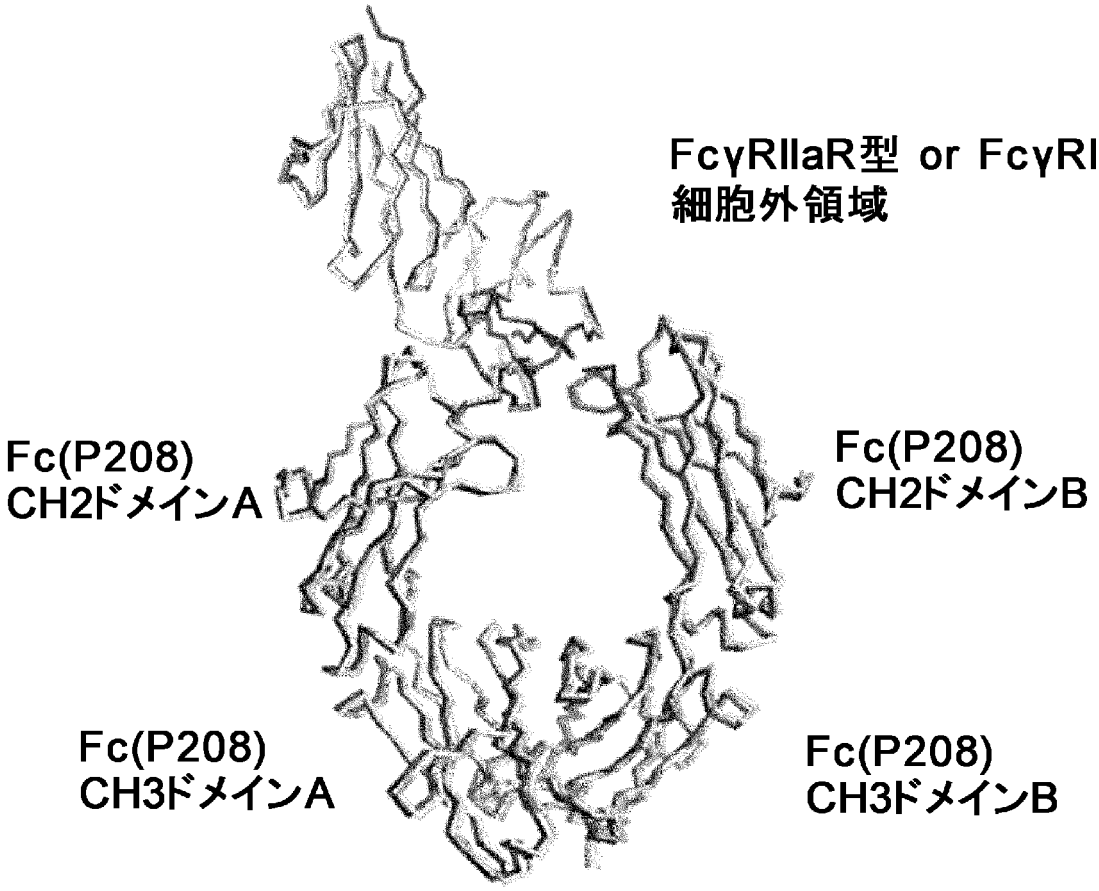
細線: Fc(P238D)/FcγRIIb 細胞外領域複合体X線結晶構造
太線: Fc(P208)/FcγRIIb 細胞外領域複合体X線結晶構造

[図10]



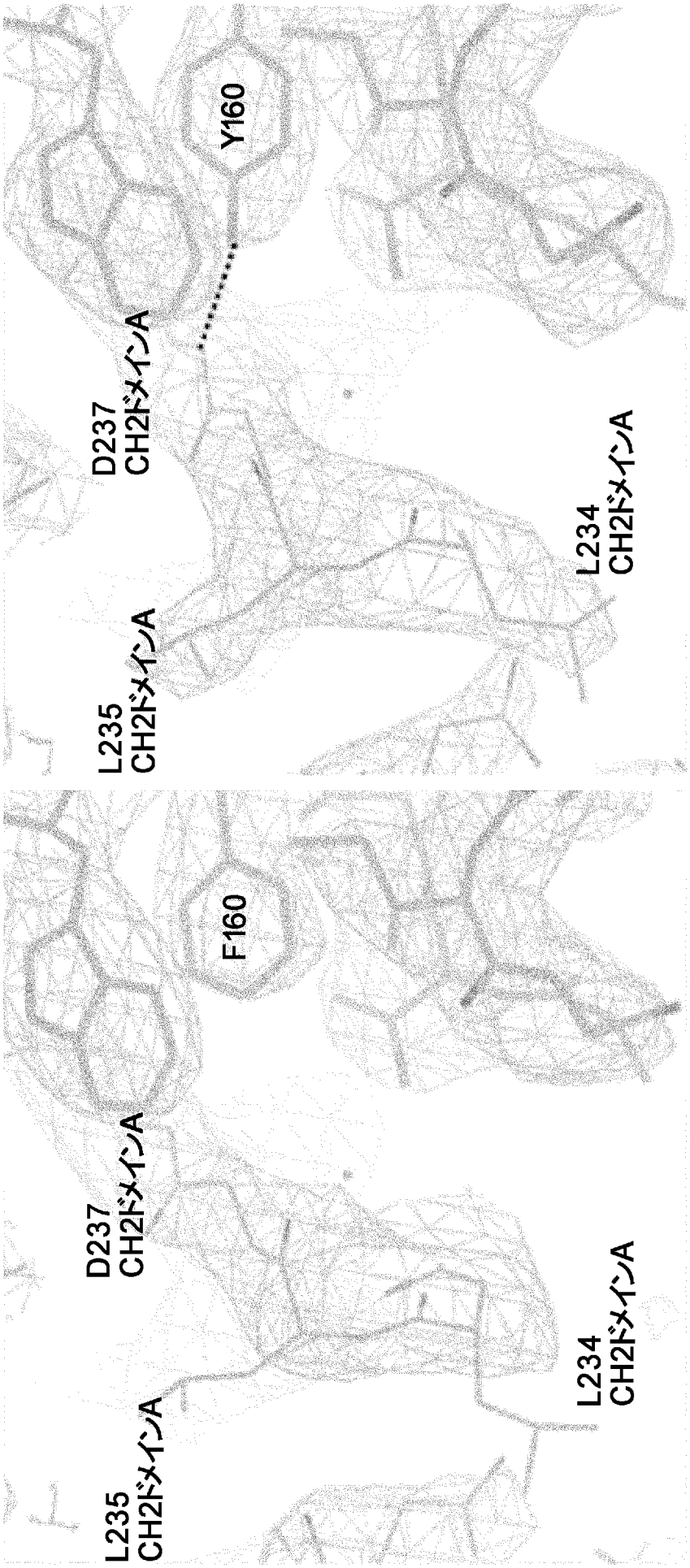
細線: Fc(P208)、太線: FcγRIIb細胞外領域

[図11]



黒色: Fc(P208)/FcγRIIaR型 細胞外領域複合体X線結晶構造
灰色: Fc(P208)/FcγRIIb 細胞外領域複合体X線結晶構造

[図12]

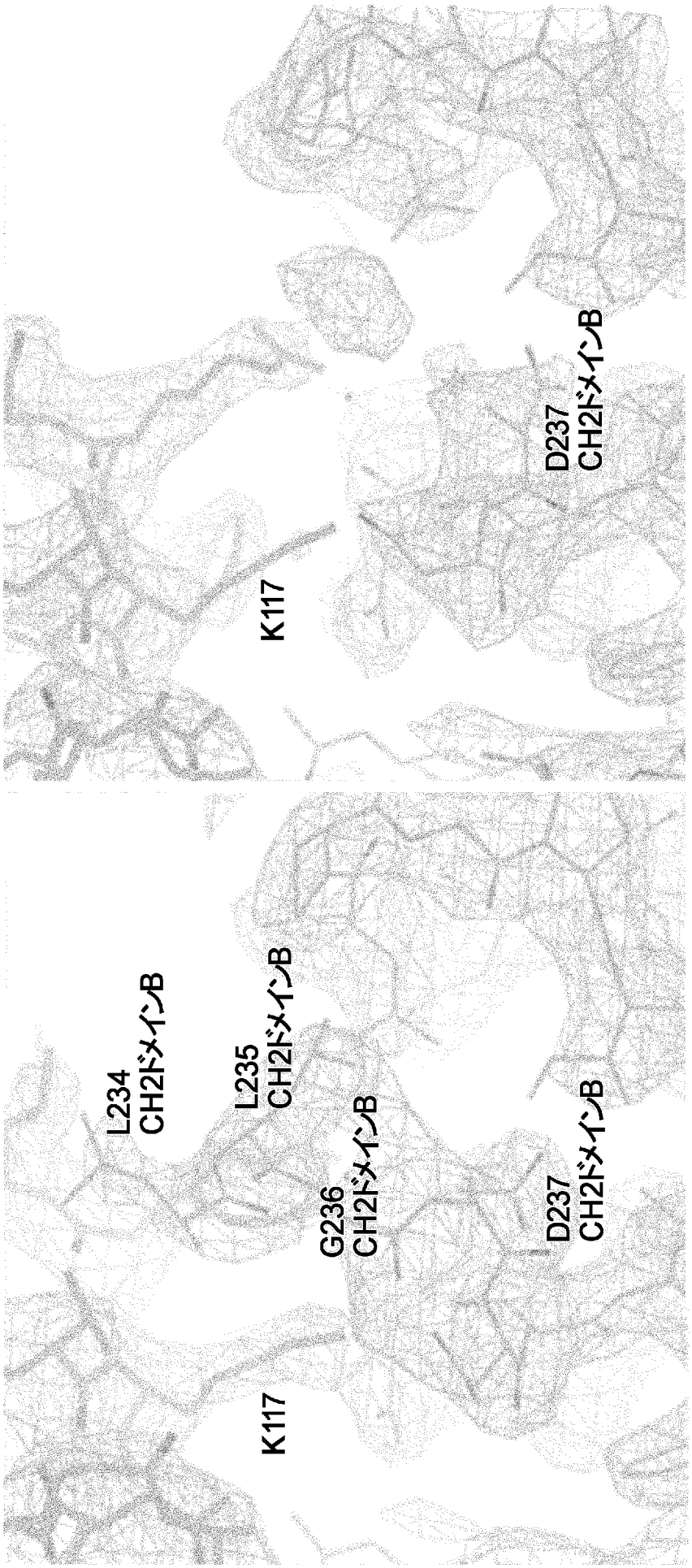


細線: Fc(P208)、太線: FcγRIIaR型 or FcγRIIb細胞外領域

左: Fc(P208)/FcγRIIaR型 細胞外領域複合体X線結晶構造

右: Fc(P208)/FcγRIIb 細胞外領域複合体X線結晶構造

[図13]

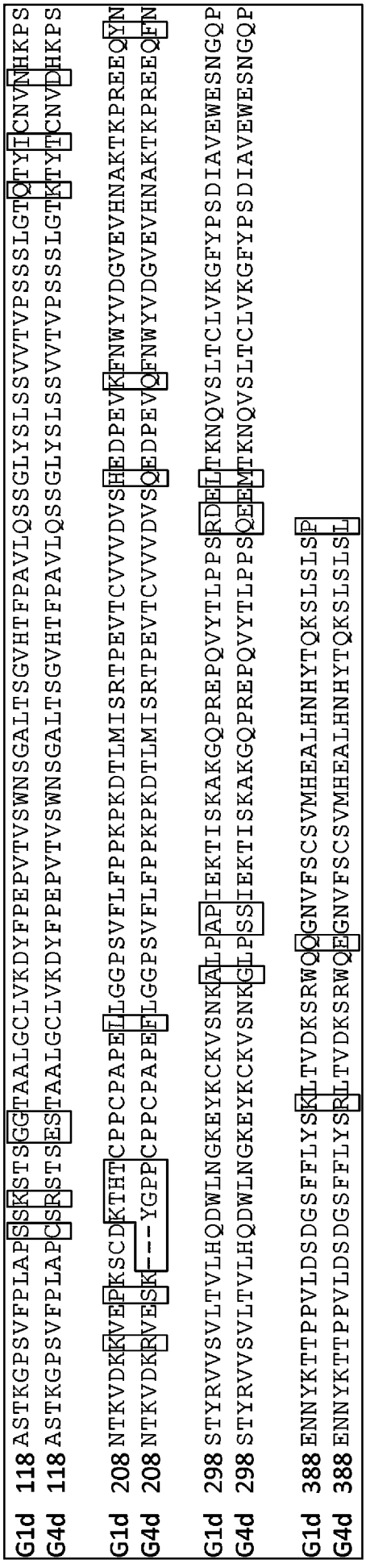


細線: Fc(P208)、太線: FcγRIIaR型 or FcγRIIb細胞外領域

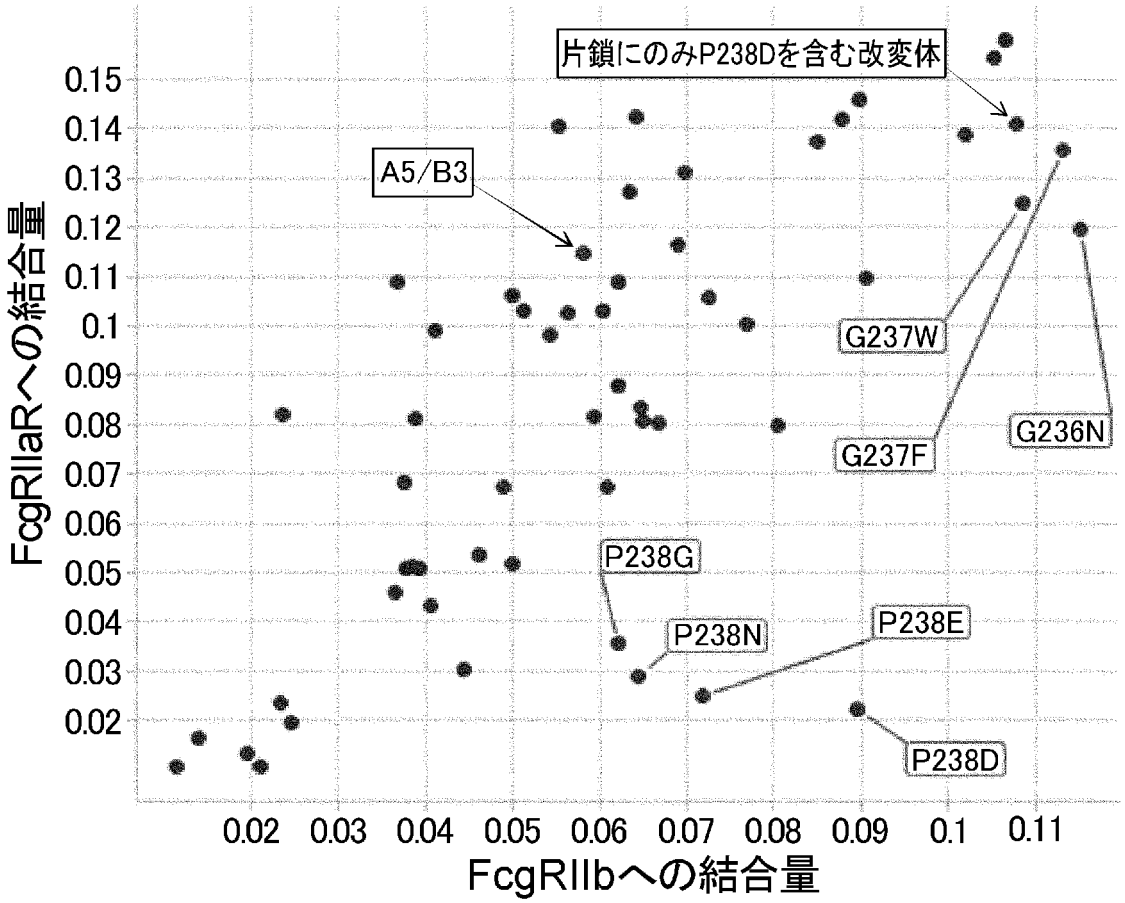
左: Fc(P208)/FcγRIIaR型 細胞外領域複合体X線結晶構造

右: Fc(P208)/FcγRIIb 細胞外領域複合体X線結晶構造

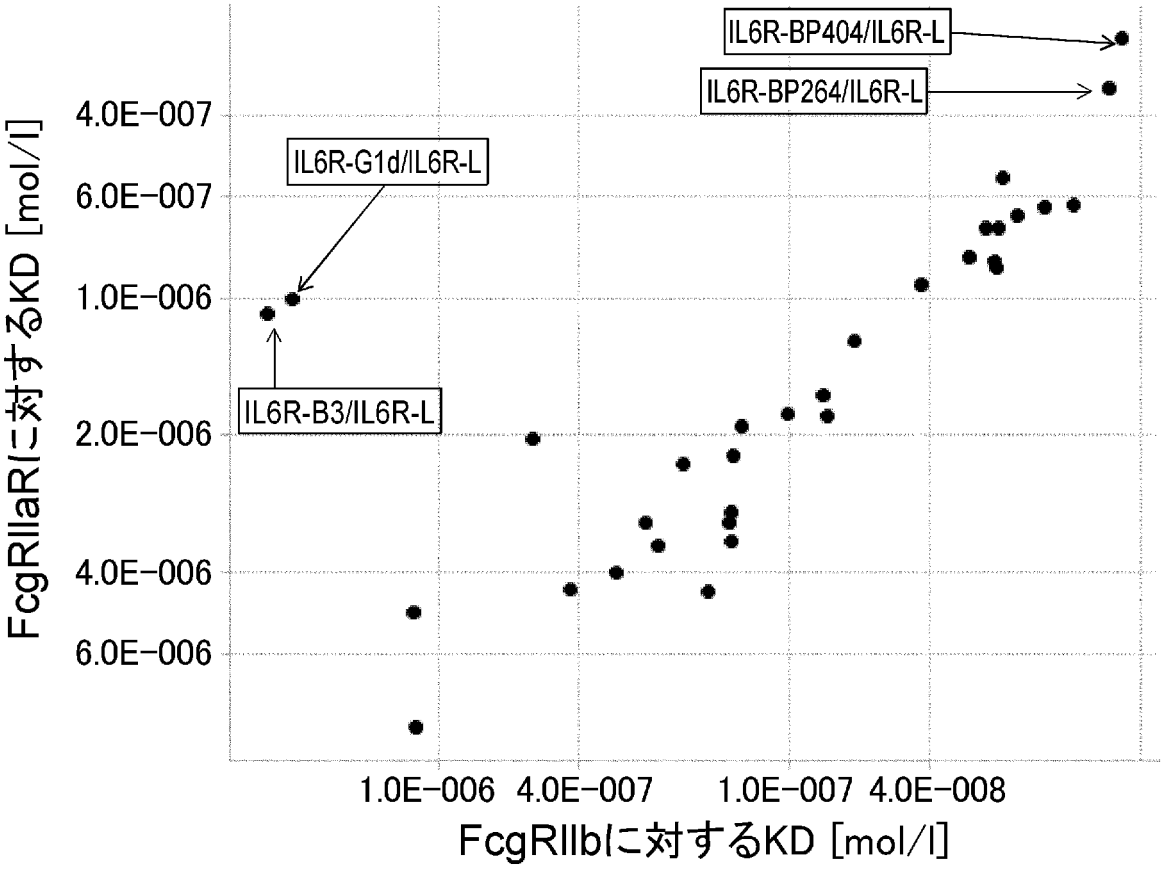
[図14]


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

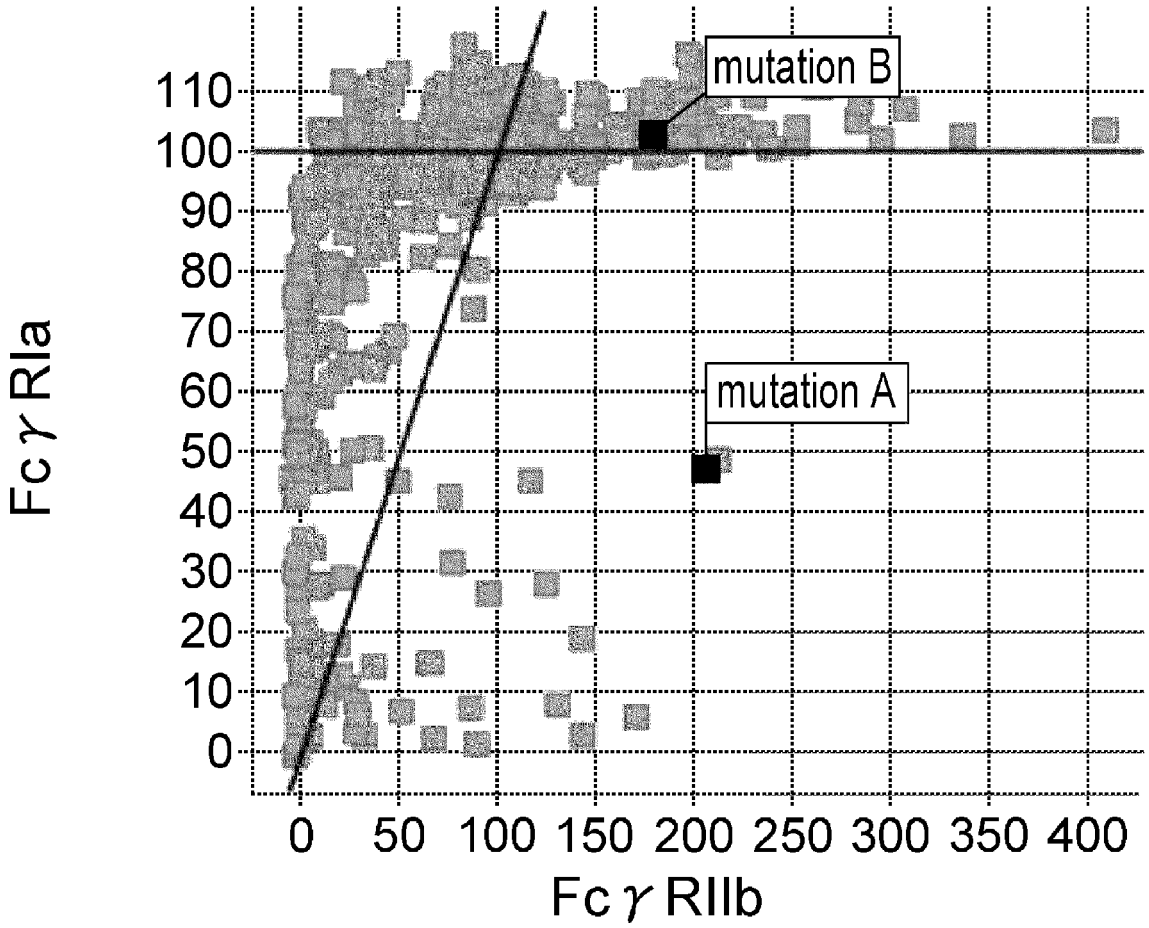
[図15]


片鎖にのみP238Dを含む改変体
A5/B3
G237W
G237F
G236N
P238G
P238N
P238E
P238D
FcgRIIaRへの結合量
FcgRIIbへの結合量
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

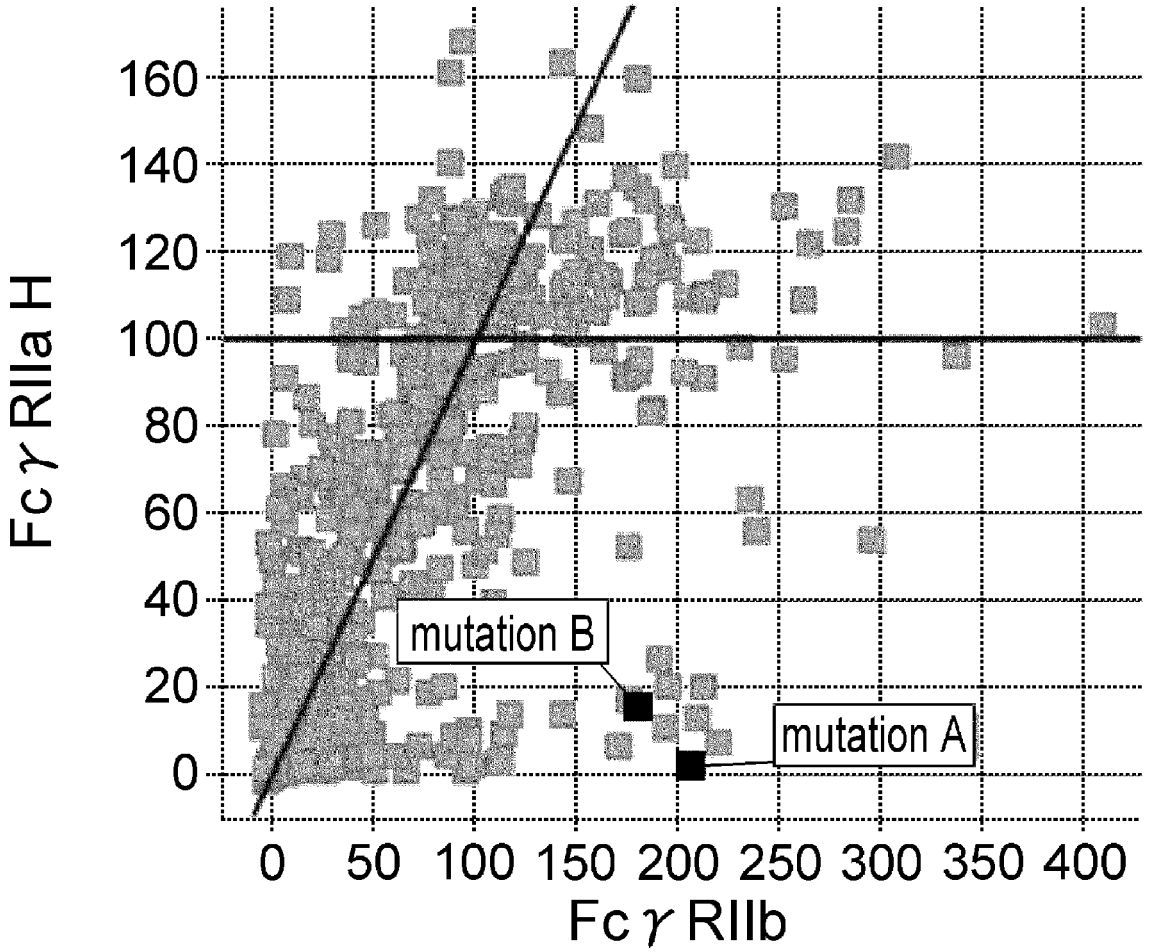
[図16]


IL6R-BP404/IL6R-L
IL6R-BP264/IL6R-L
IL6R-G1d/IL6R-L
IL6R-B3/IL6R-L
FcgRIIaRに対するKD [mol/l]
FcgRIIbに対するKD [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

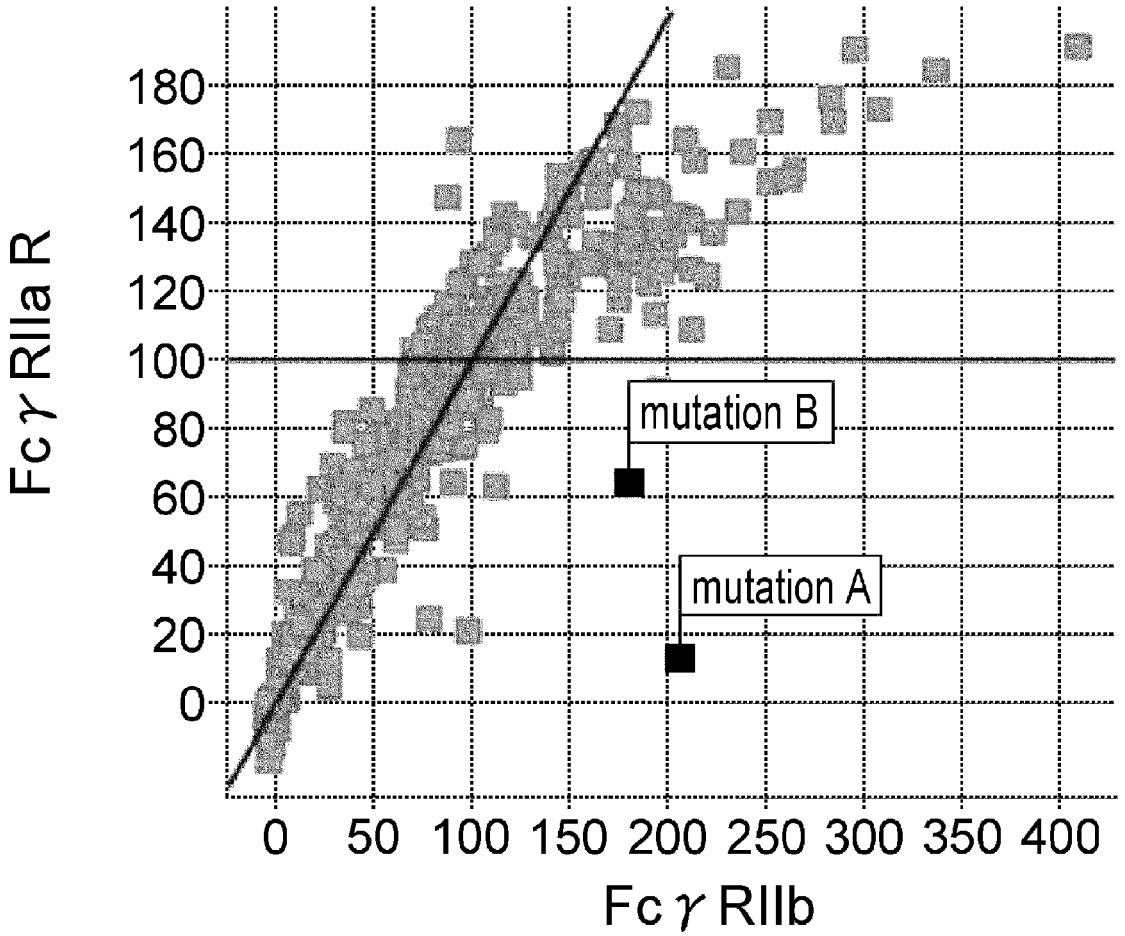
[図17]


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
FcγRIa
FcγRIIb

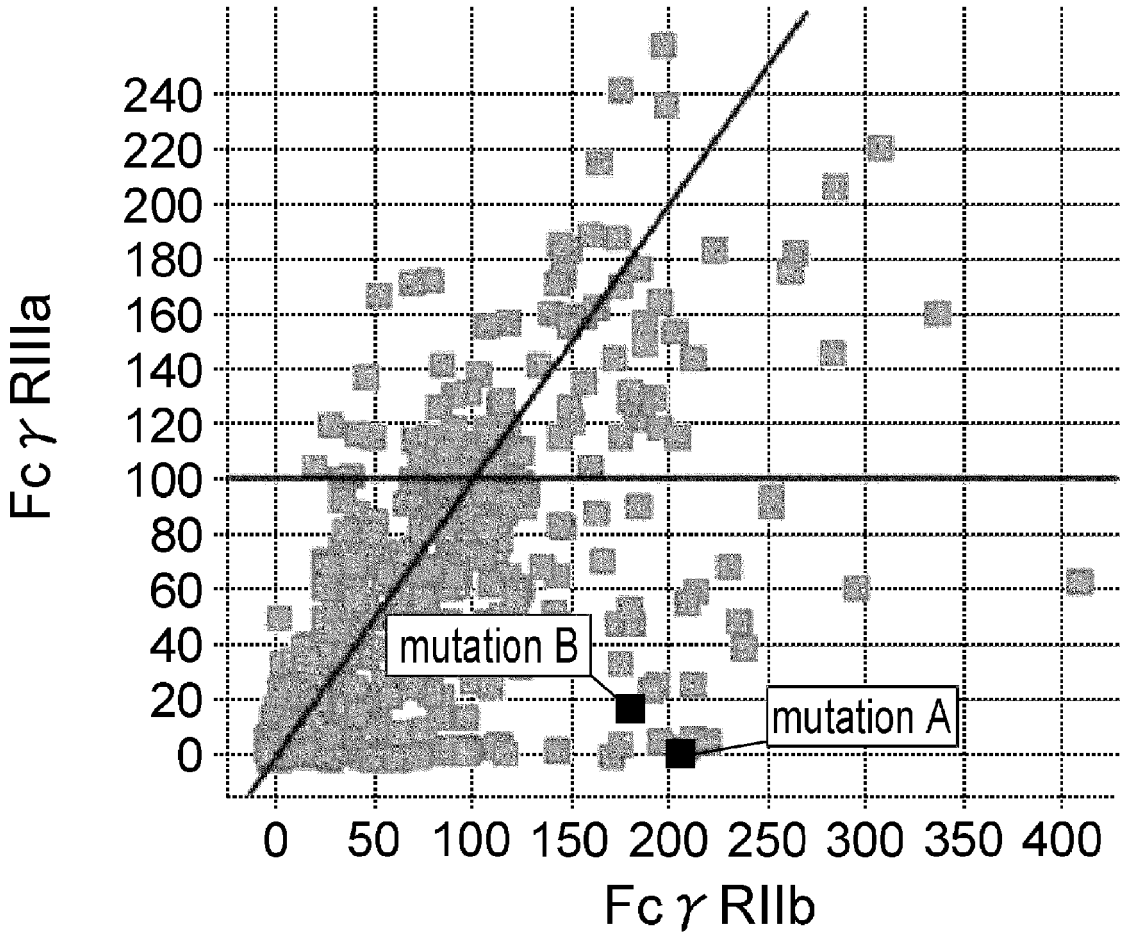
[図18]


mutation B
mutation A
160
140
120
100
80
60
40
20
0
0 50 100 150 200 250 300 350 400
FcγRIIa H
FcγRIIb

[図19]


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

[図20]


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

[図21]

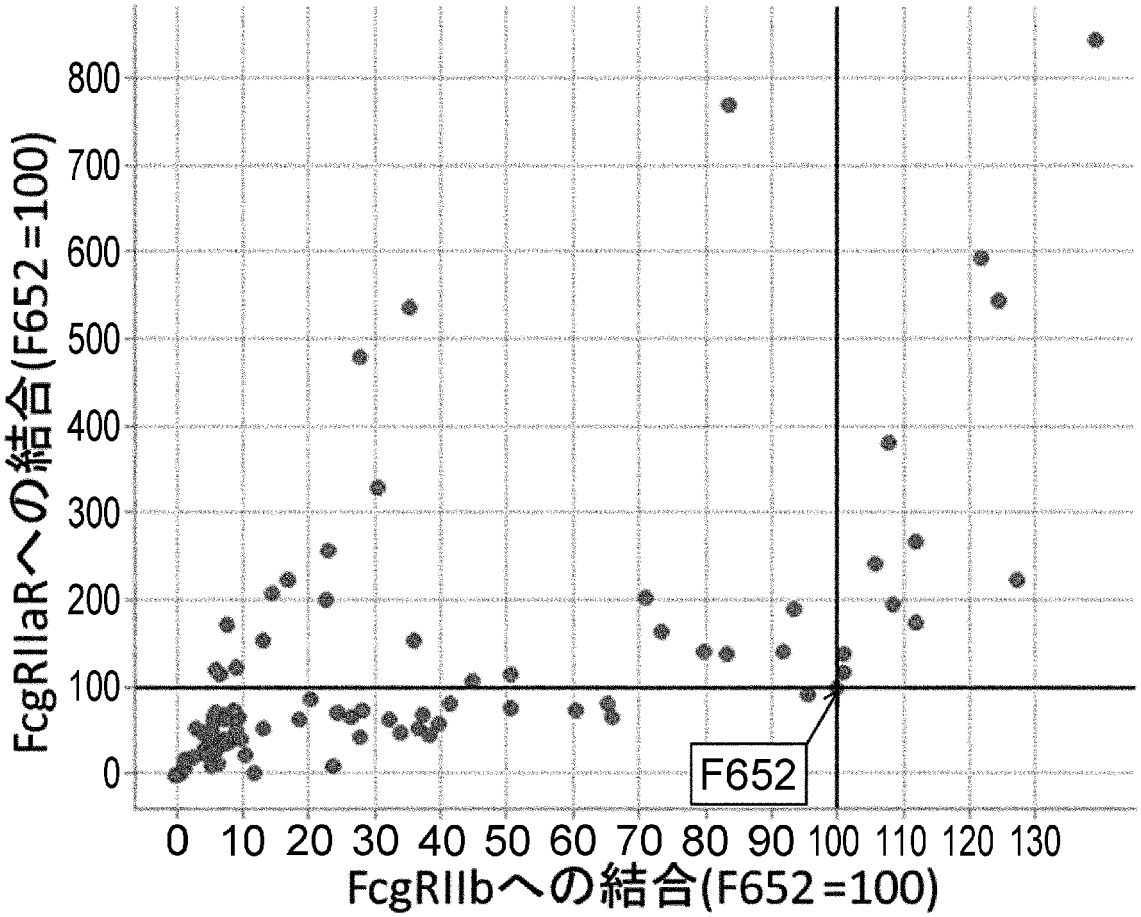
```
              1                                                                                 2
EU index      1-2---------3---------4---------5---------6---------7---------8---------9---------0---------1---------2-
              8-0---------0---------0---------0---------0---------0---------0---------0---------0---------0---------0-
IgG1          ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD-
IgG2          ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCV-
IgG3          ASTKGPSVFPLAPCSRSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVNHKPSNTKVDKRVELKTPLG
IgG4          ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGP-

               2
EU index       2------                                              -3---------4---------5---------6---------7---------8
               2-----8                                              -0---------0---------0---------0---------0---------0
IgG1          -KTHTCPP---------------------------------------------CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
IgG2          -E---CPP---------------------------------------------CPAPPVA-GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVD
IgG3          DTTHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFKWYVD
IgG4          -P---CPS---------------------------------------------CPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD

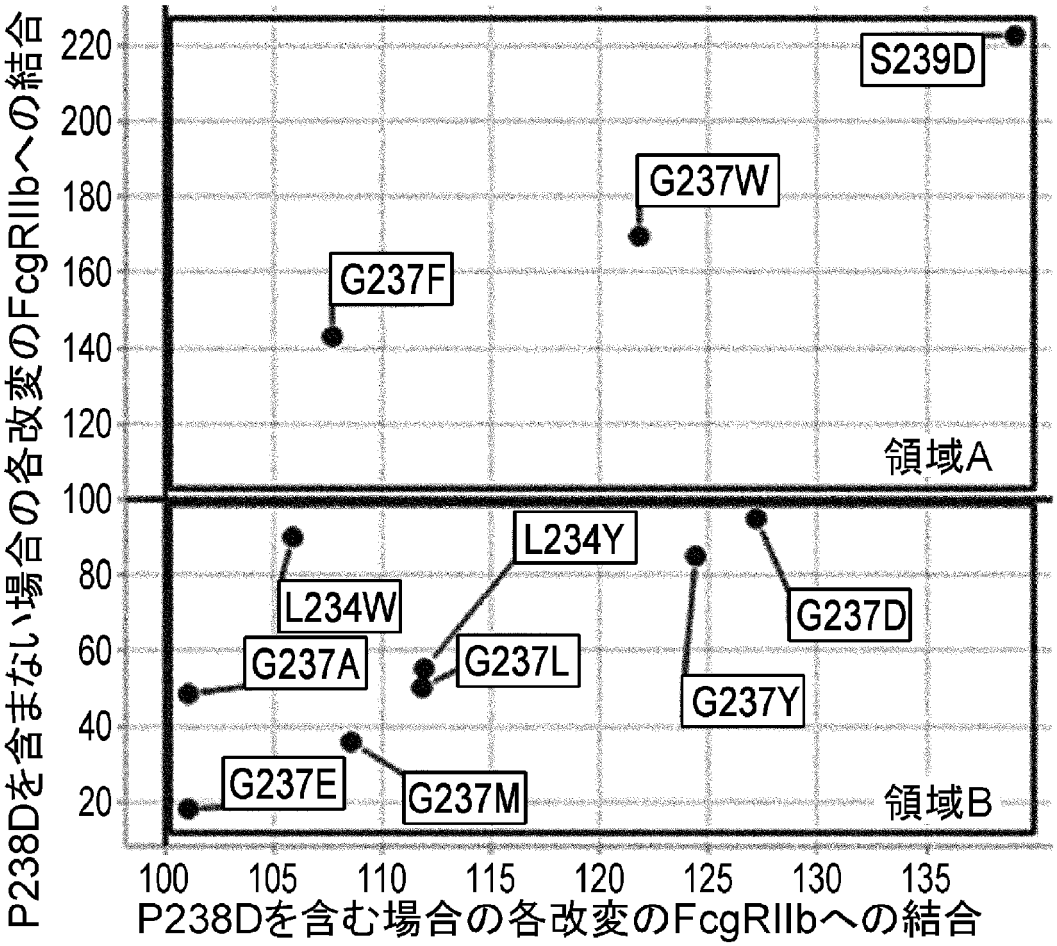
              2                  3
EU index      8--------9---------0---------1---------2---------3---------4---------5---------6---------7---------8-----
              1--------0---------0---------0---------0---------0---------0---------0---------0---------0---------0-----
IgG1          GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNG
IgG2          GVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG
IgG3          GVEVHNAKTKPREEQYNSTFRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESSG
IgG4          GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNG

              3             4
EU index      8---9---------0---------1---------2---------3---------4-------
              6---0---------0---------0---------0---------0---------0------7
IgG1          QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK  (配列番号：11)
IgG2          QPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK  (配列番号：12)
IgG3          QPENNYNTTPPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK  (配列番号：13)
IgG4          QPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK  (配列番号：14)
```

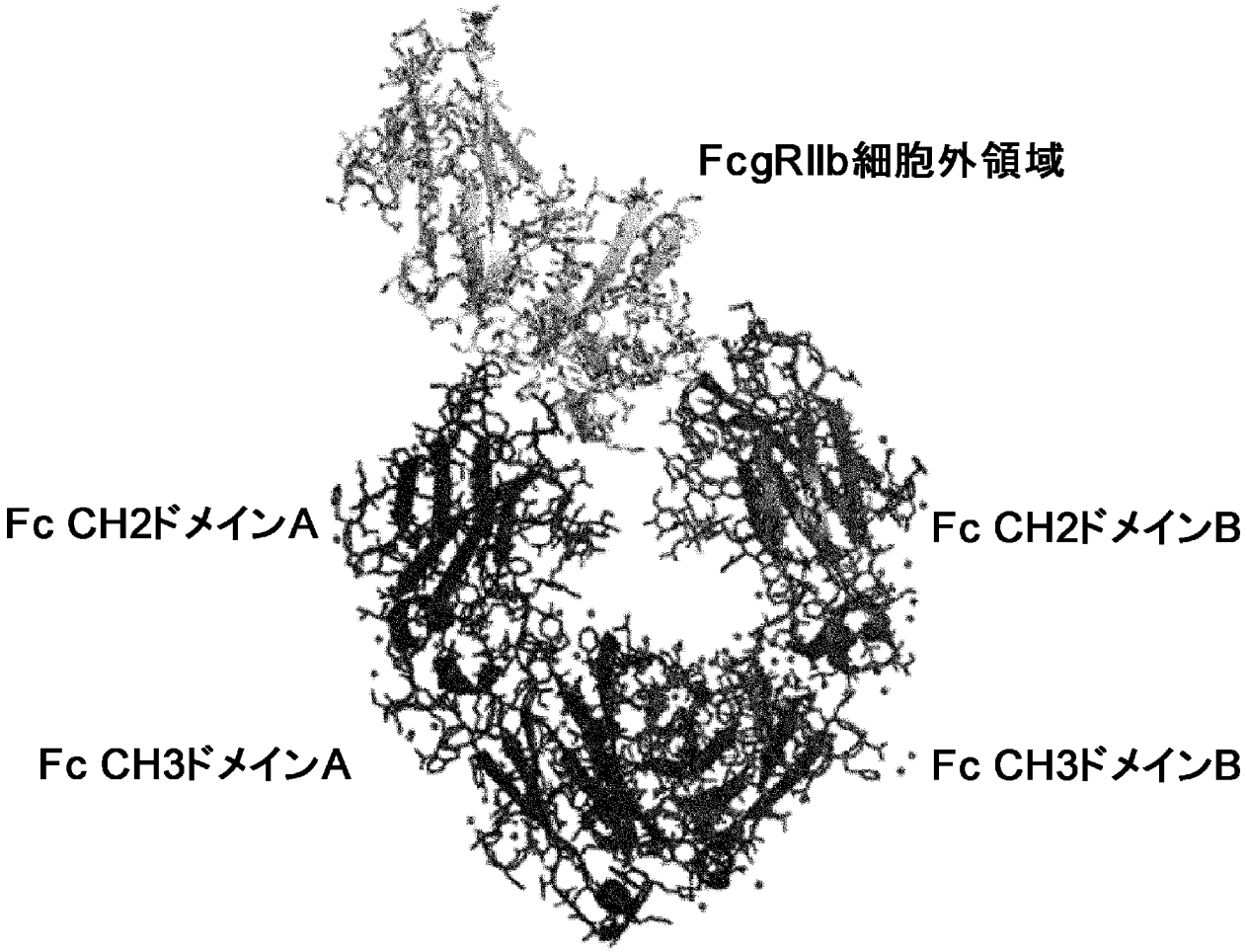
[図22]


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

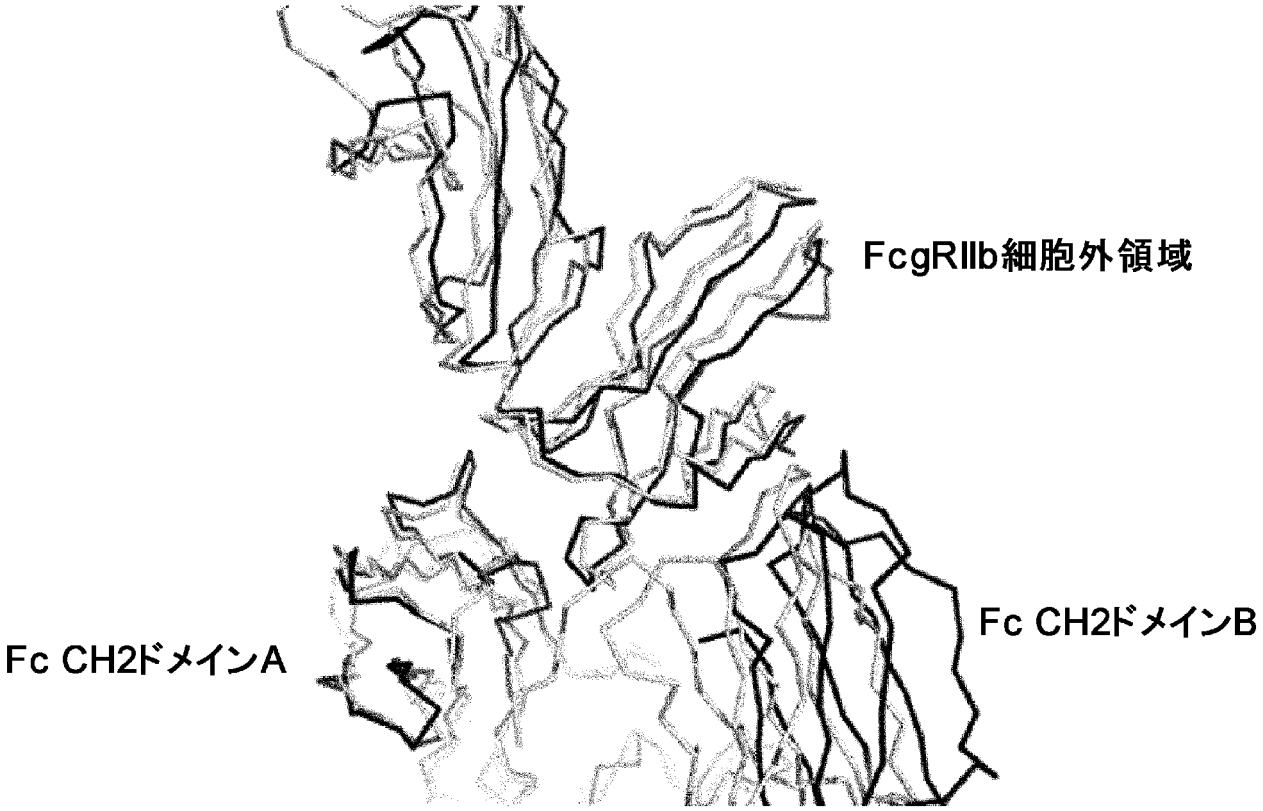
[図23]


P238Dを含まない場合の各改変のFcgRIIbへの結合
P238Dを含む場合の各改変のFcgRIIbへの結合
S239D
G237W
G237F
領域A
L234Y
L234W
G237D
G237A
G237L
G237Y
G237E
G237M
領域B
20
40
60
80
100
120
140
160
180
200
220
100 105 110 115 120 125 130 135

[図24]

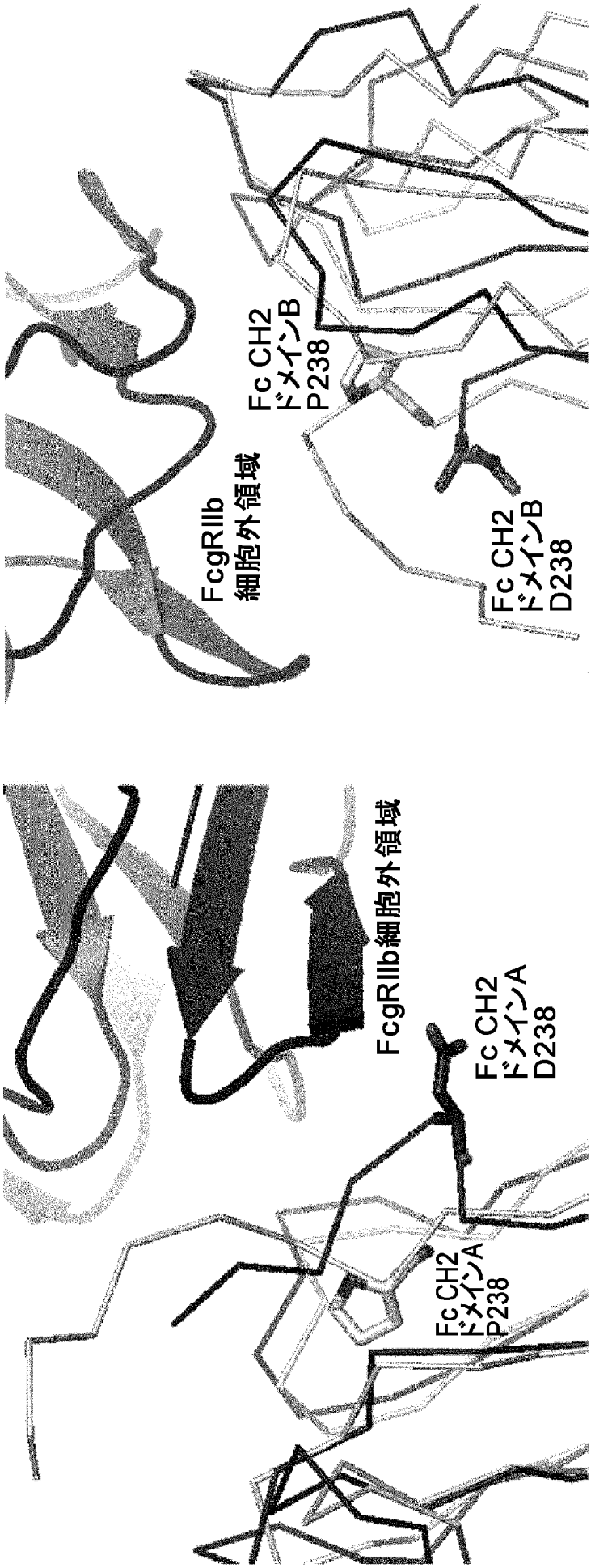


[図25]



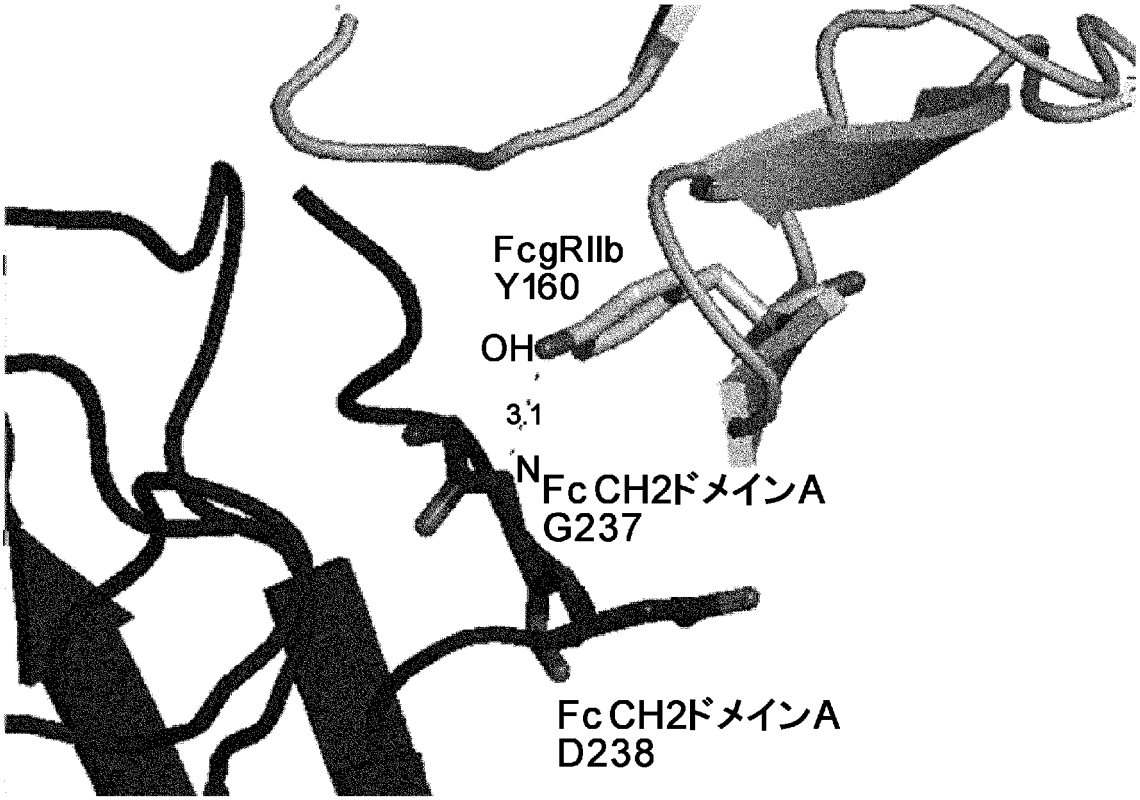
黒　Fc(P238D)/FcγRIIb細胞外領域複合体の結晶構造
灰色 Fc(WT)/FcγRIIb細胞外領域複合体のモデル構造

[図26]

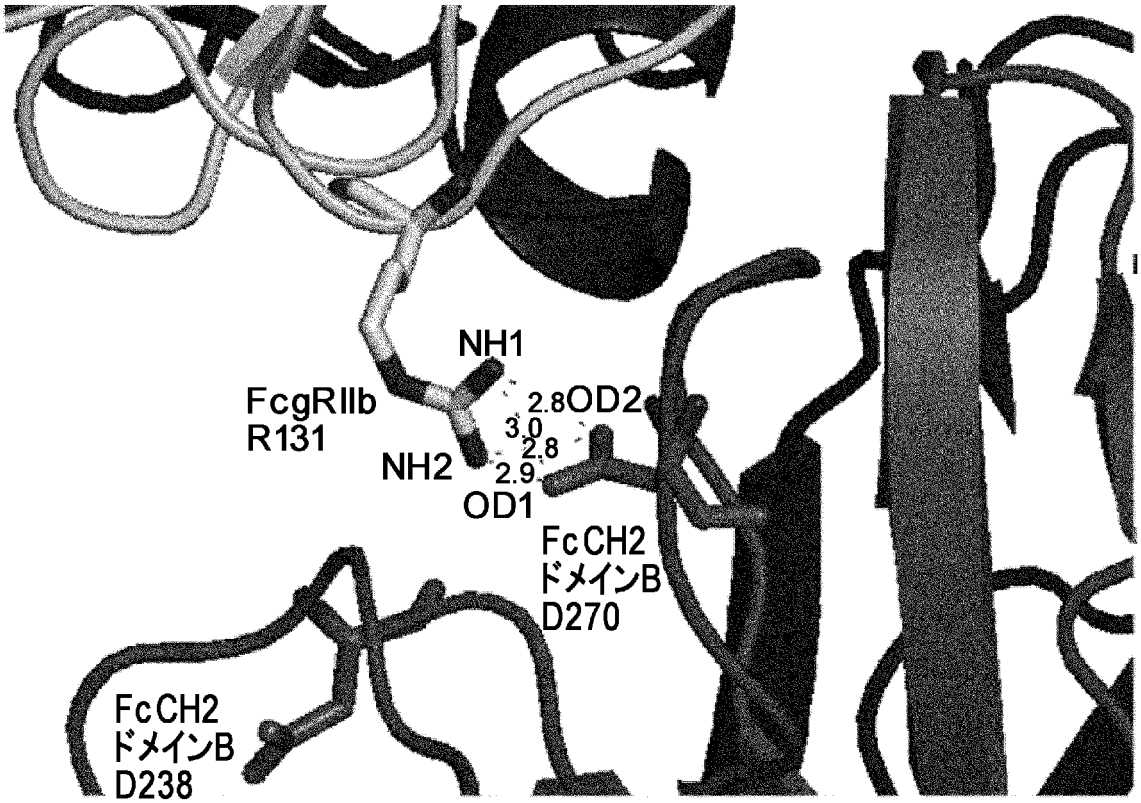


黒　Fc(P238D)/FcγRIIb細胞外領域複合体の結晶構造
灰色 Fc(WT)/FcγRIIb細胞外領域複合体のモデル構造

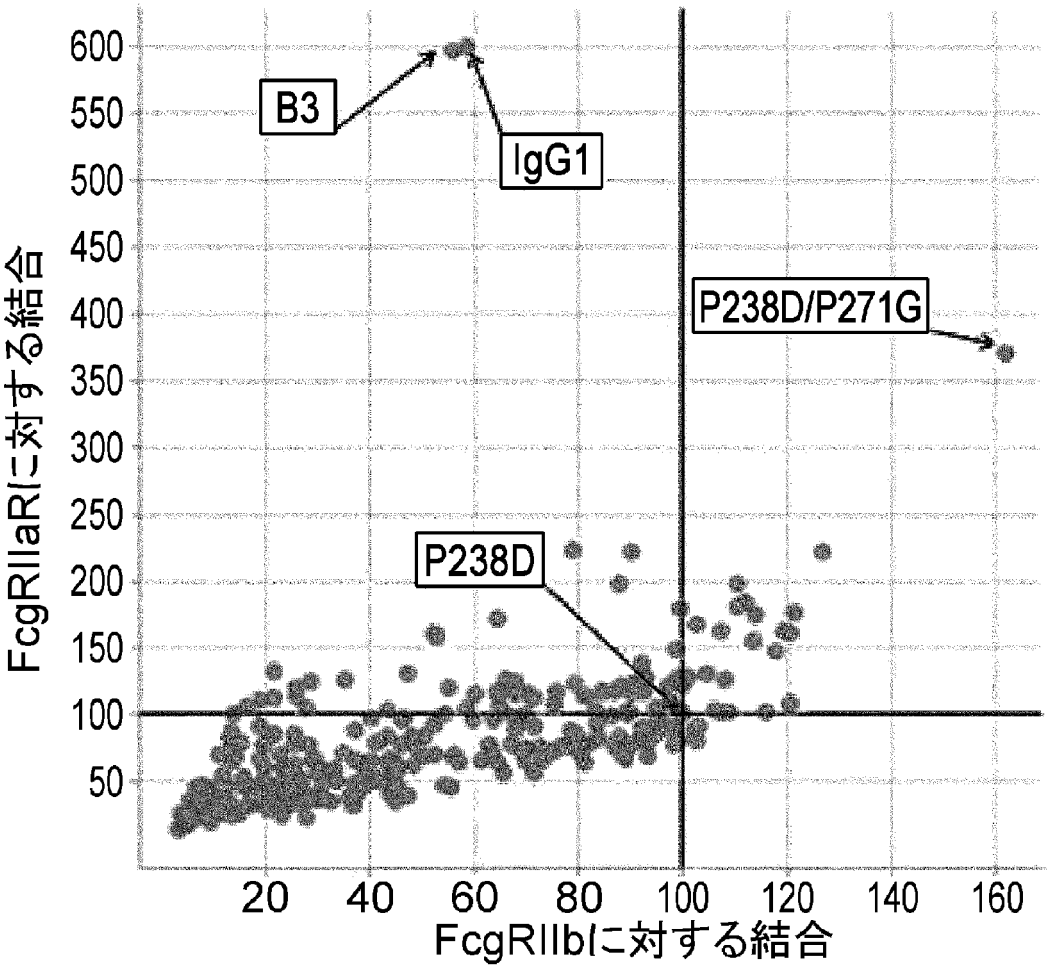
[図27]


FcgRIIb
Y160
OH
3.1
N
Fc CH2ドメインA
G237
Fc CH2ドメインA
D238

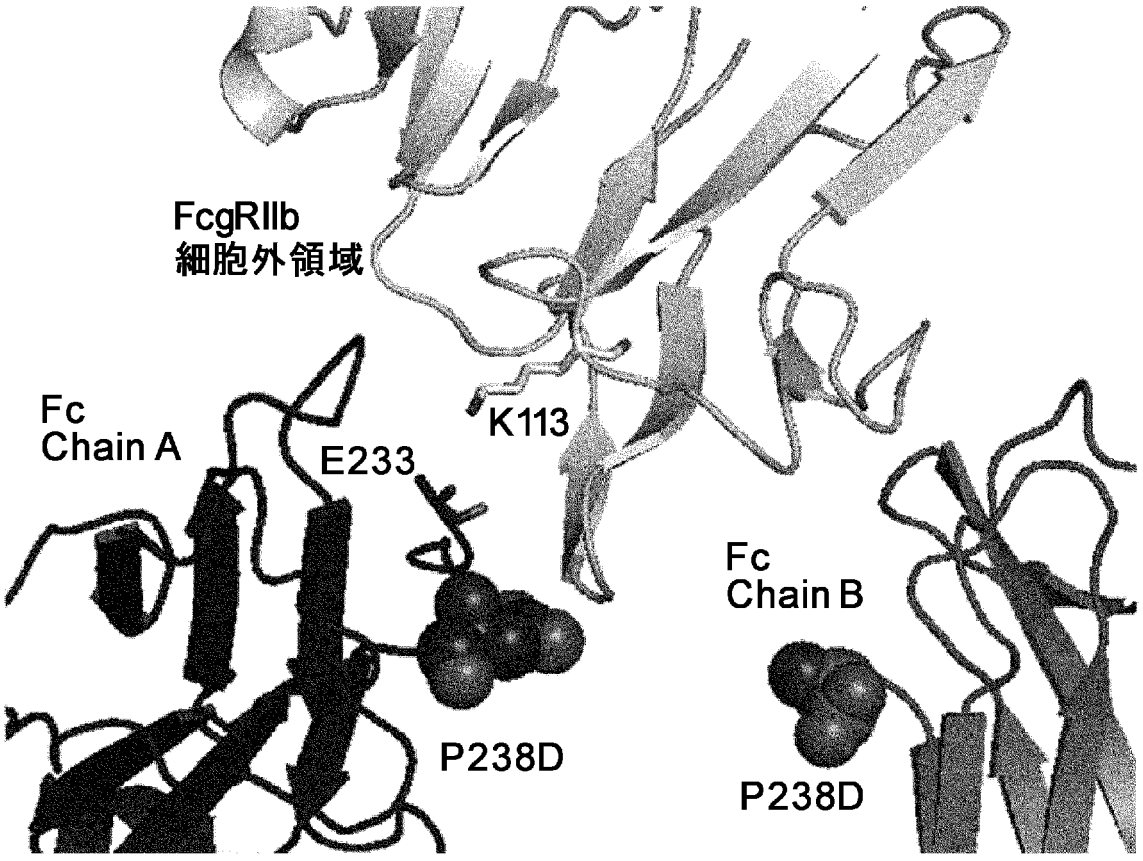
[図28]


NH1
FcgRIIb
R131
2.8
OD2
3.0
2.8
NH2
2.9
OD1
Fc CH2
ドメインB
D270
Fc CH2
ドメインB
D238

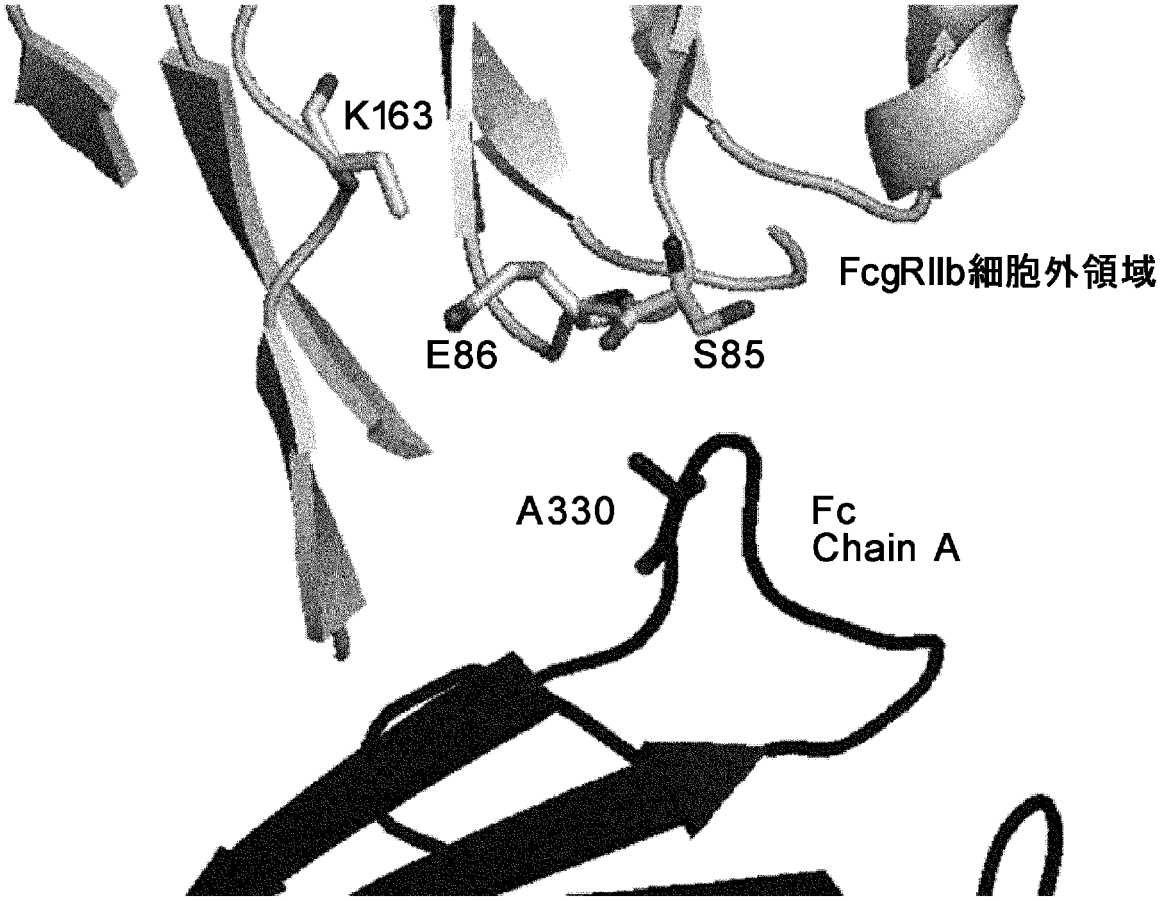
[図29]


B3
IgG1
P238D/P271G
P238D
FcgRIIaRに対する結合
FcgRIIbに対する結合
600
550
500
450
400
350
300
250
200
150
100
50
20
40
60
80
100
120
140
160

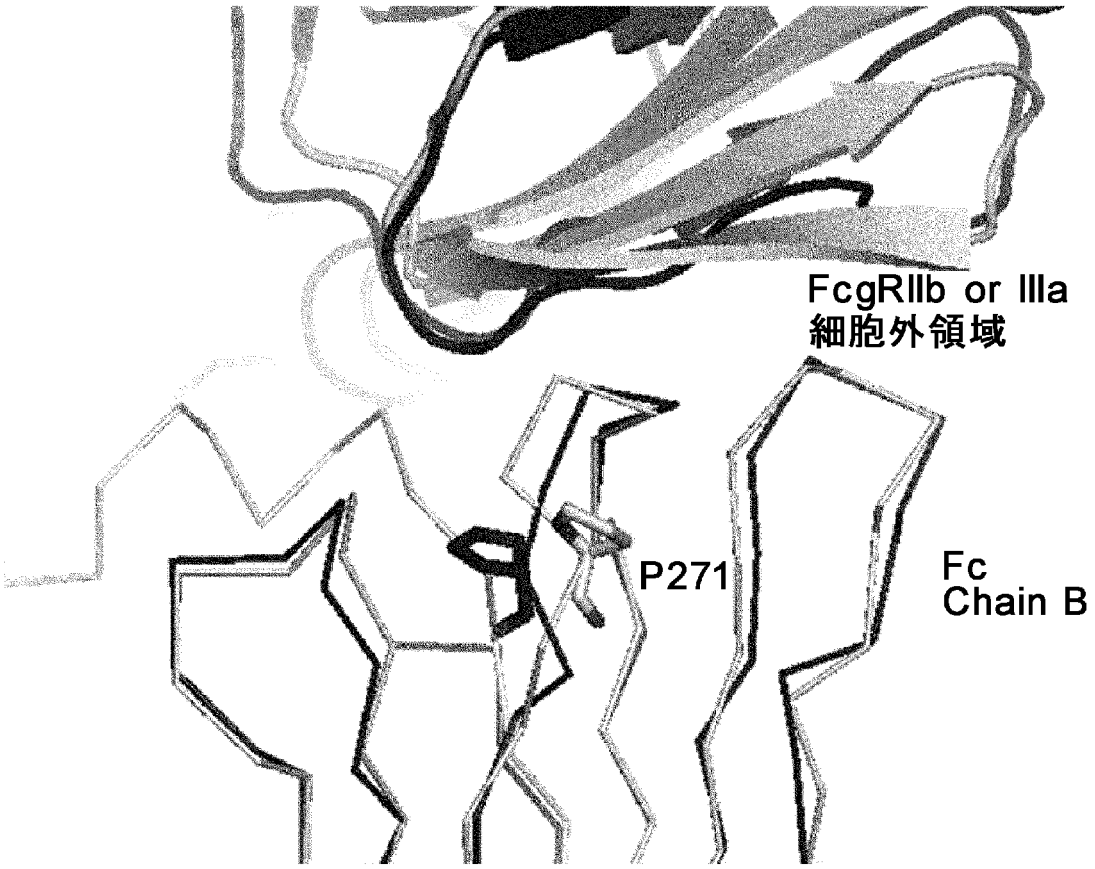
[図30]


FcgRIIb
細胞外領域
Fc
Chain A
E233
K113
Fc
Chain B
P238D
P238D

[図31]

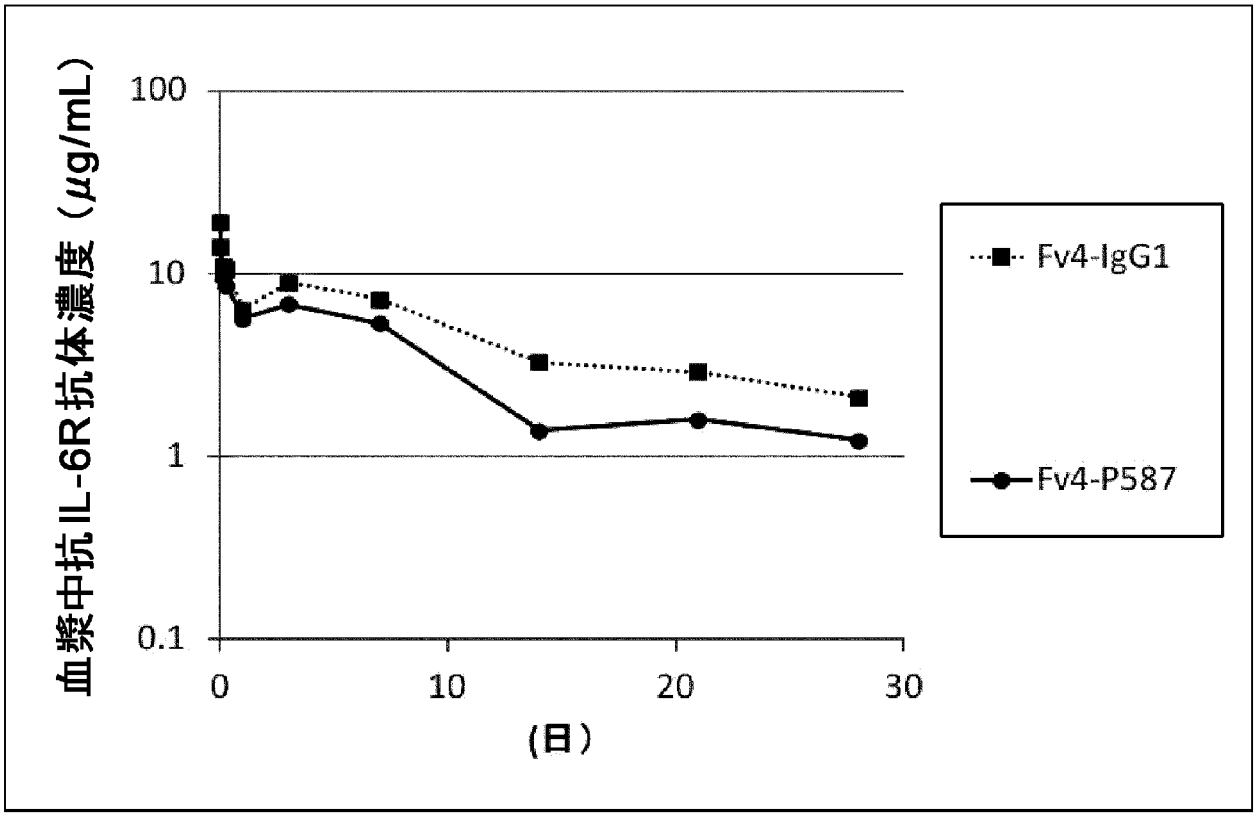


[図32]

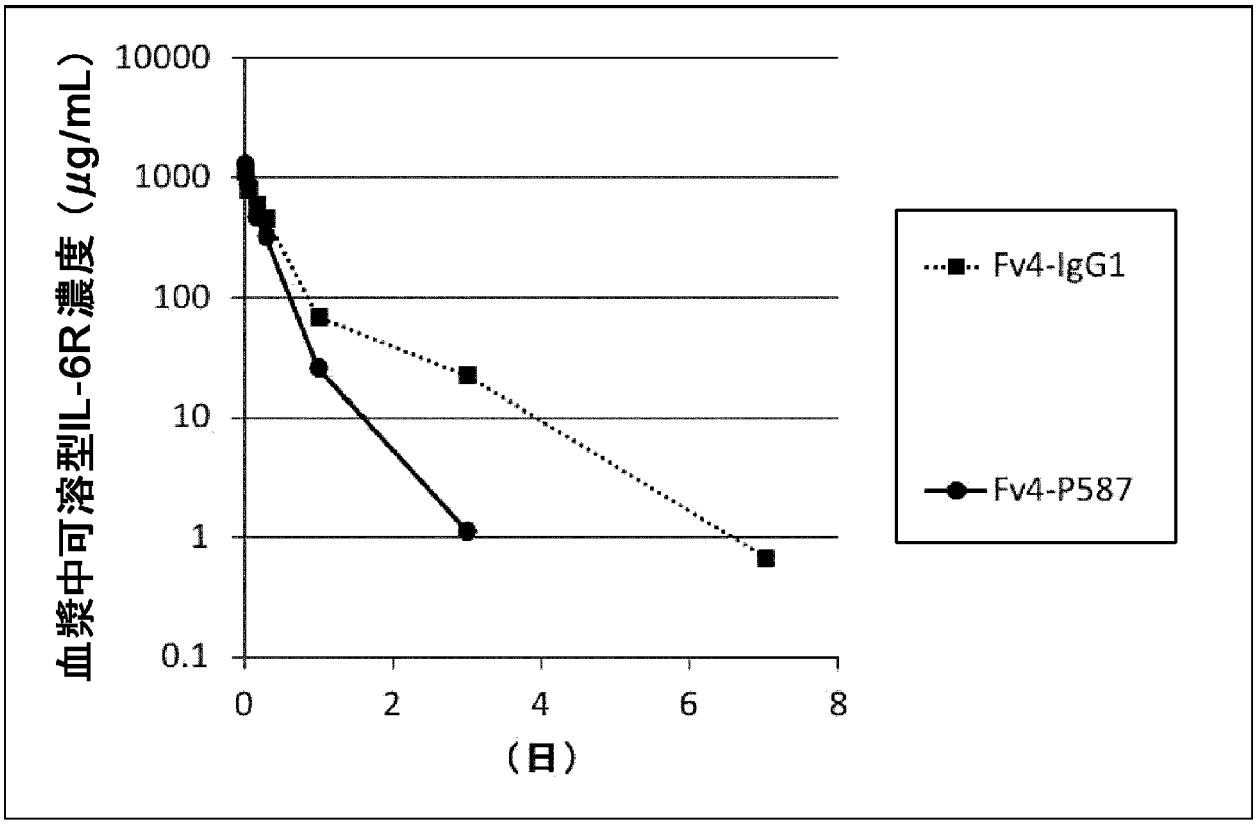


黒　Fc(P238D)/FcγRIIb細胞外領域複合体の結晶構造
灰色　Fc(WT)/FcγRIIIa細胞外領域複合体の結晶構造(PDB code:3SGJ)

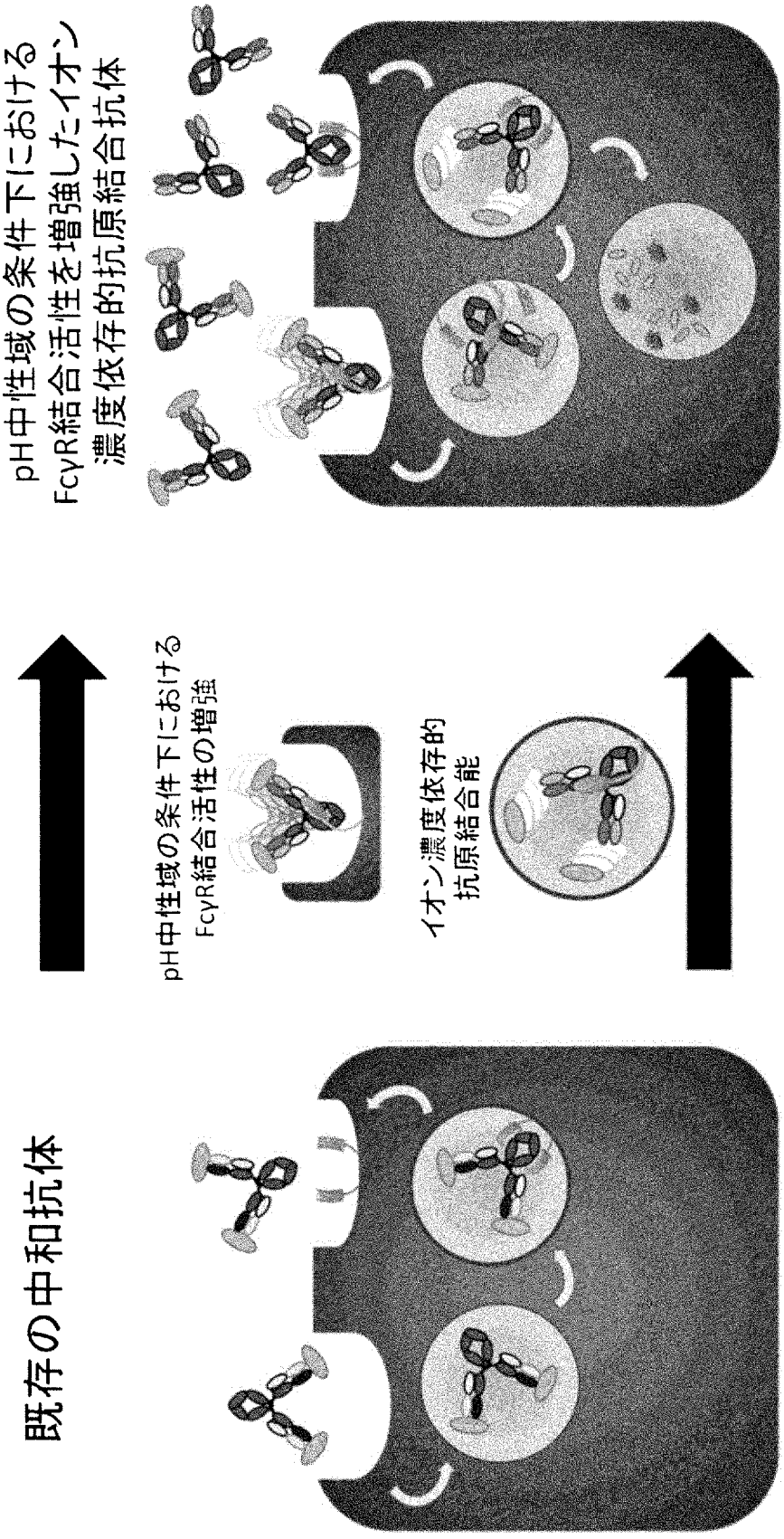
[図33]


血漿中抗IL-6R抗体濃度（μg/mL）
100
10
1
0.1
0
10
20
30
（日）
Fv4-IgG1
Fv4-P587

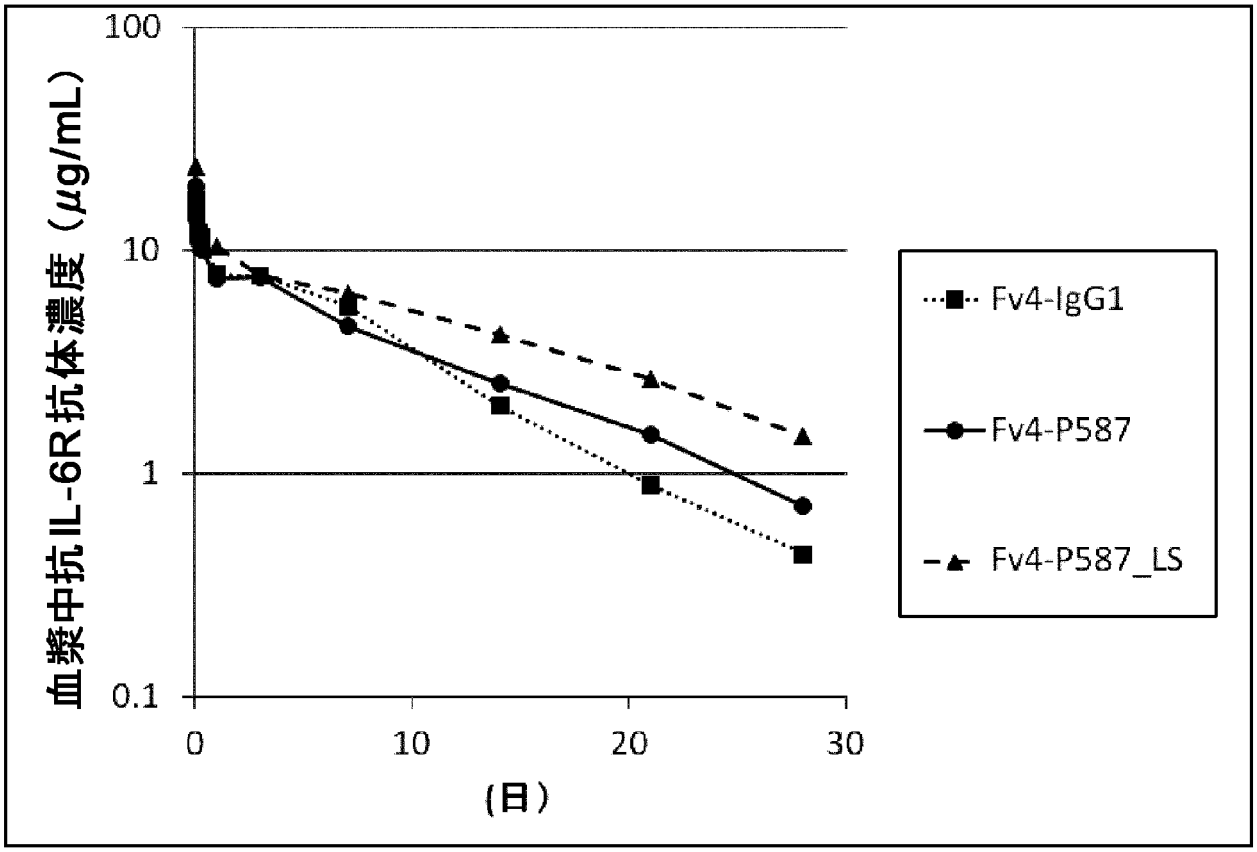
[図34]


血漿中可溶型IL-6R濃度（μg/mL）
10000
1000
100
10
1
0.1
0
2
4
6
8
（日）
Fv4-IgG1
Fv4-P587

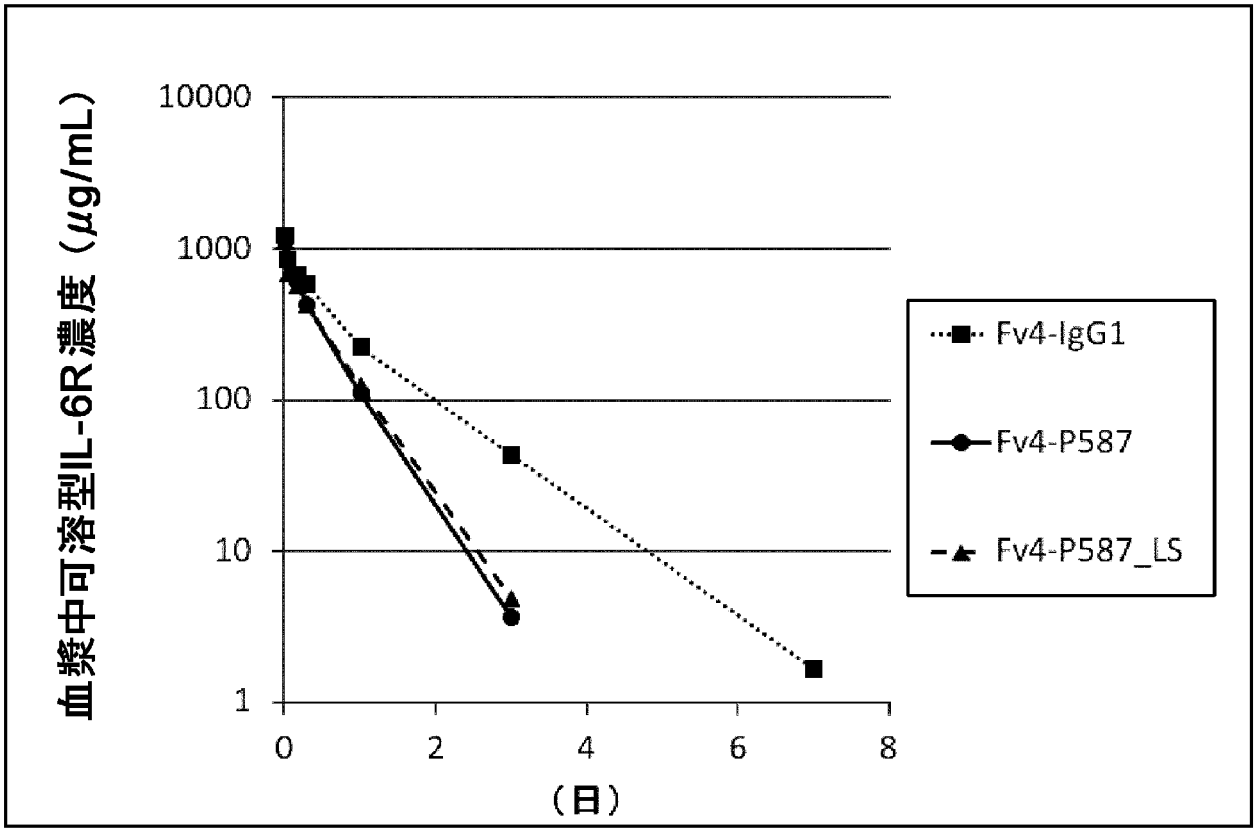
[図35]


既存の中和抗体
pH中性域の条件下におけるFcγR結合活性の増強
イオン濃度依存的抗原結合能
pH中性域の条件下におけるFcγR結合活性を増強したイオン濃度依存的抗原結合抗体

[図36]


100
10
1
0.1
0
10
20
30
血漿中抗IL-6R抗体濃度（μg/mL）
(日)
Fv4-IgG1
Fv4-P587
Fv4-P587_LS

[図37]


10000
1000
100
10
1
0
2
4
6
8
血漿中可溶型IL-6R濃度（μg/mL）
(日)
Fv4-IgG1
Fv4-P587
Fv4-P587_LS