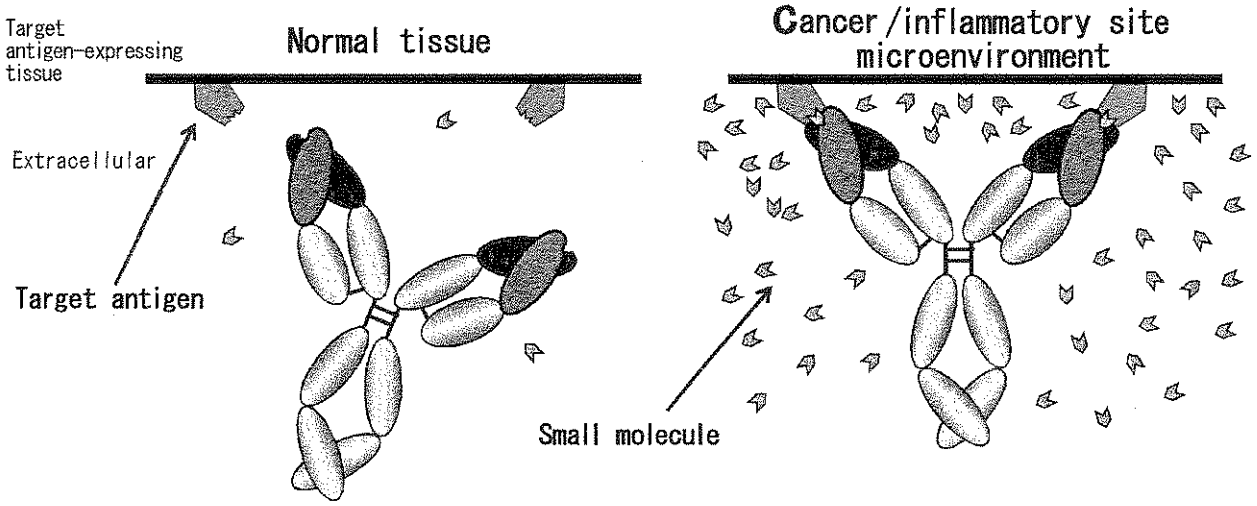

Target antigen-expressing tissue
Normal tissue
Cancer/inflammatory site microenvironment
Extracellular
Target antigen
Small molecule

Fig. 1

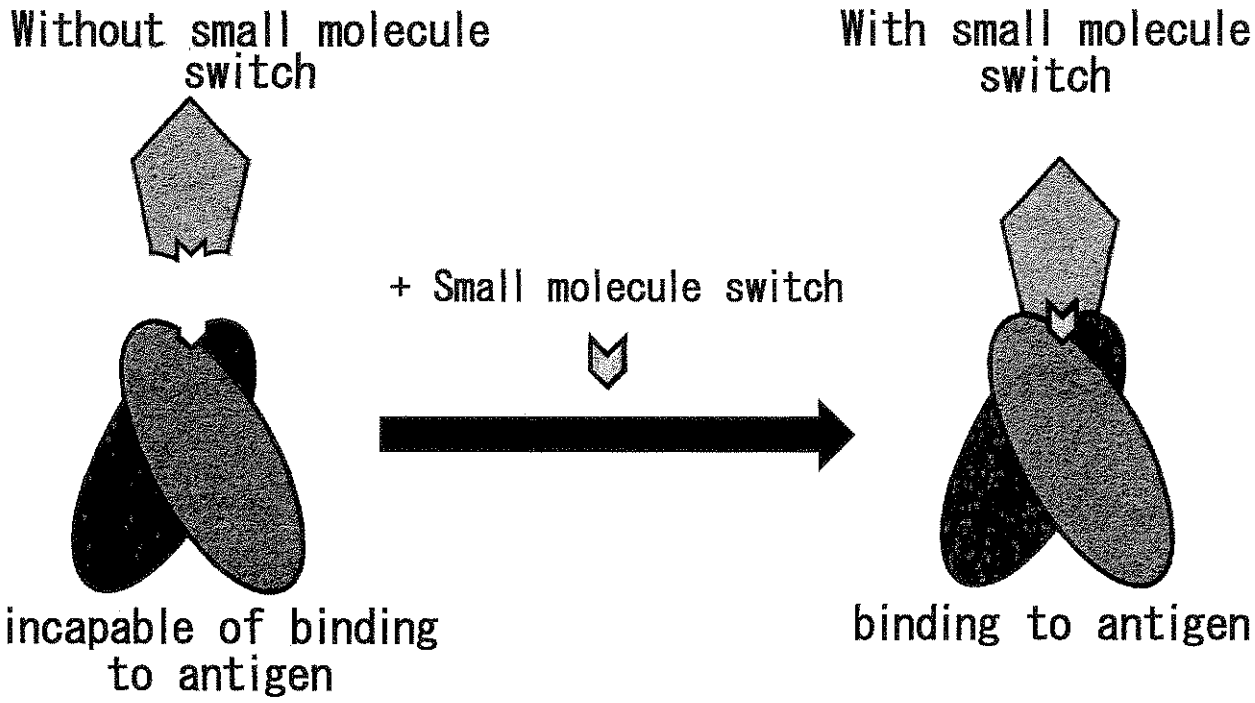

Without small molecule switch
With small molecule switch
+ Small molecule switch
incapable of binding to antigen
binding to antigen

Fig. 2

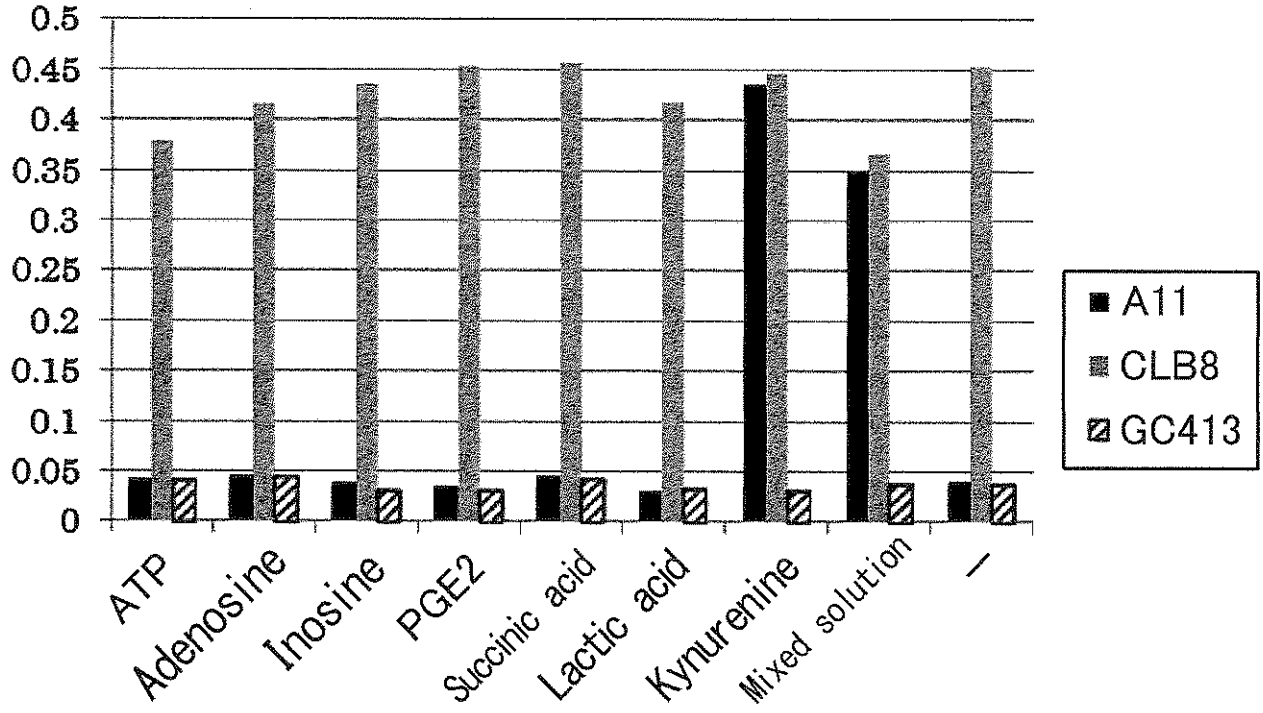

0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
ATP
Adenosine
Inosine
PGE2
Succinic acid
Lactic acid
Kynurenine
Mixed solution
—
A11
CLB8
GC413

Fig. 3

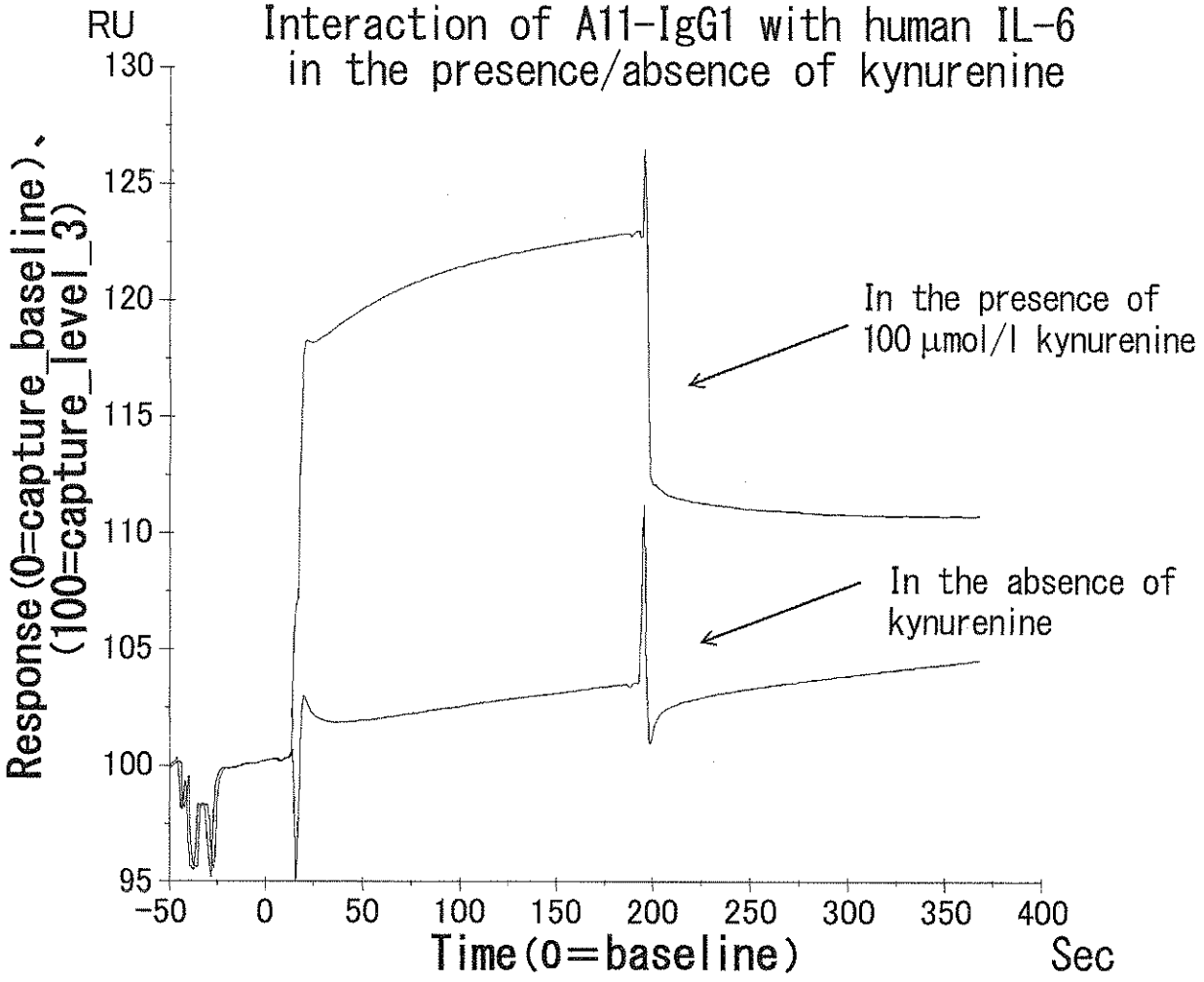

RU
Interaction of A11-IgG1 with human IL-6
in the presence/absence of kynurenine
Response(0=capture_baseline,
(100=capture_level_3)
130
125
120
115
110
105
100
95
-50
0
50
100
150
200
250
300
350
400
Time(0=baseline)
Sec
In the presence of
100 μmol/l kynurenine
In the absence of
kynurenine

Fig. 4

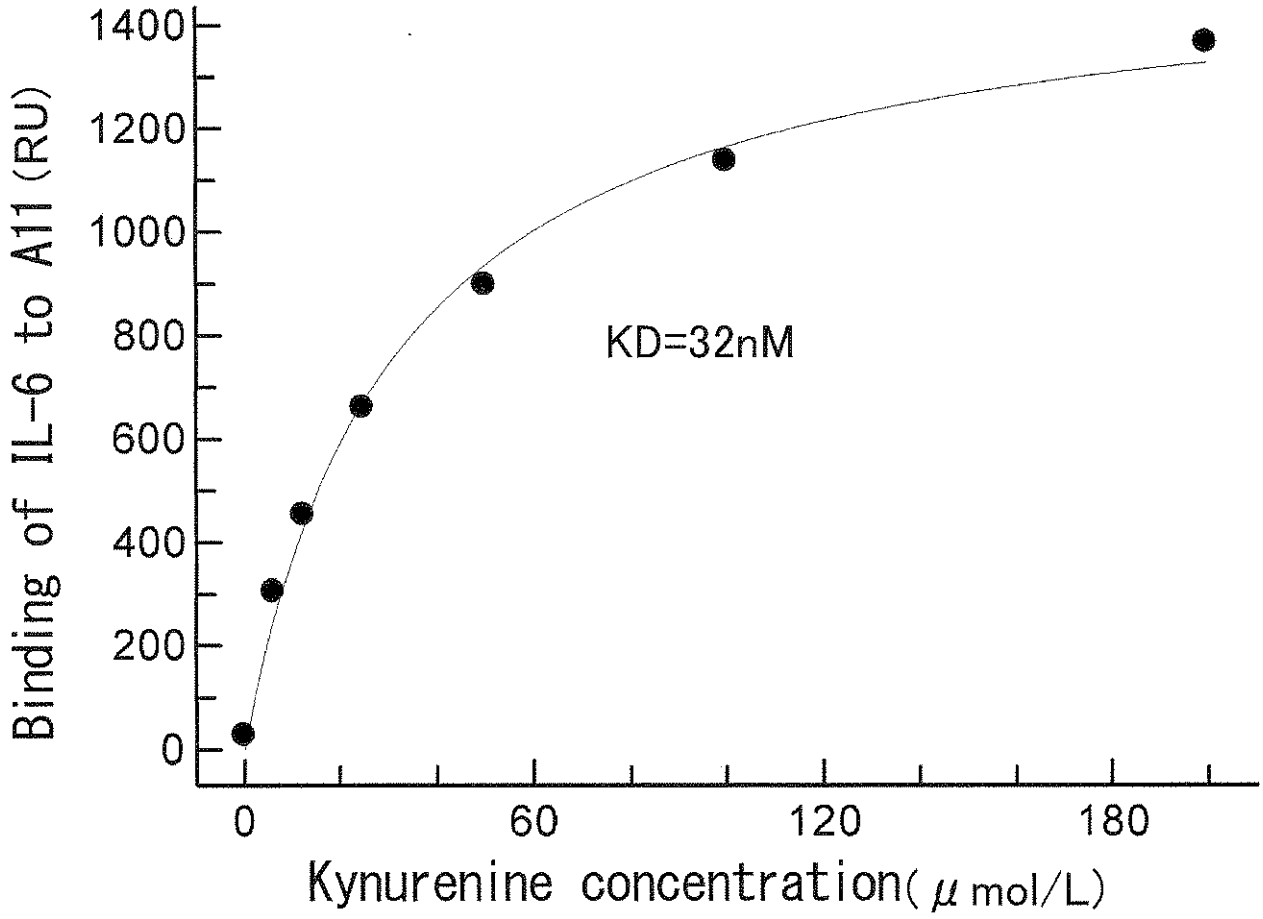

1400
1200
1000
800
600
400
200
0
Binding of IL-6 to A11 (RU)
KD=32nM
0
60
120
180
Kynurenine concentration(μ mol/L)

Fig. 5

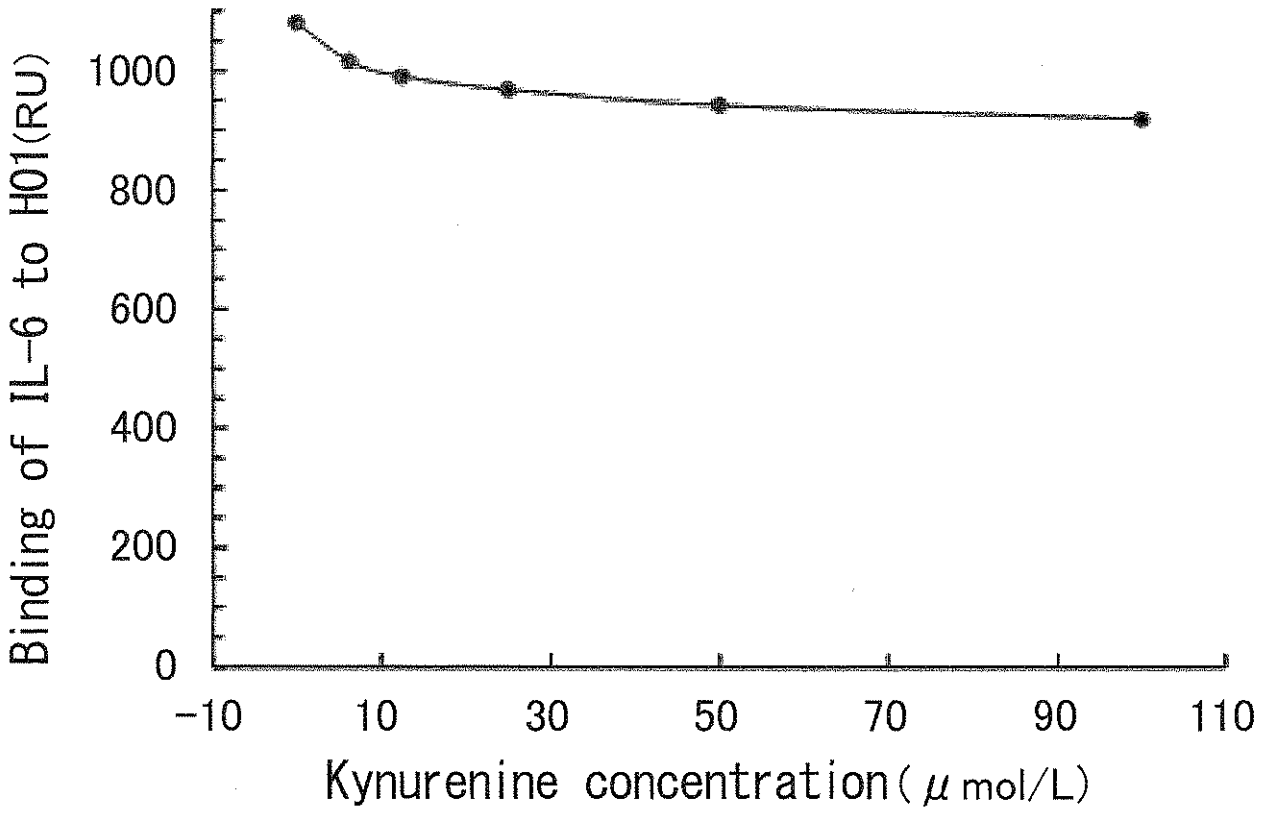

Binding of IL-6 to H01(RU)
1000
800
600
400
200
0
-10
10
30
50
70
90
110
Kynurenine concentration(μmol/L)

Fig. 6

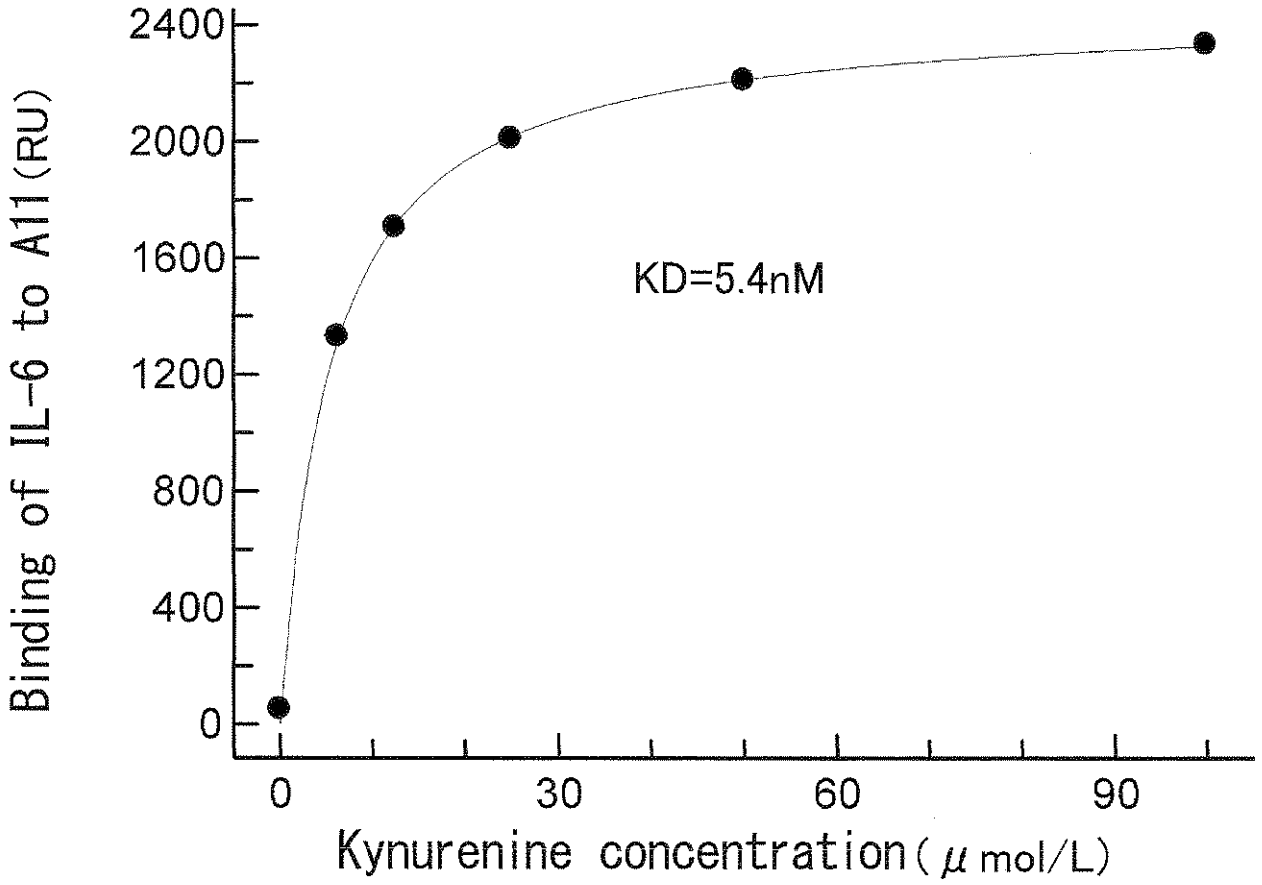

Binding of IL-6 to A11(RU)
2400
2000
1600
1200
800
400
0
KD=5.4nM
0
30
60
90
Kynurenine concentration(μmol/L)

Fig. 7

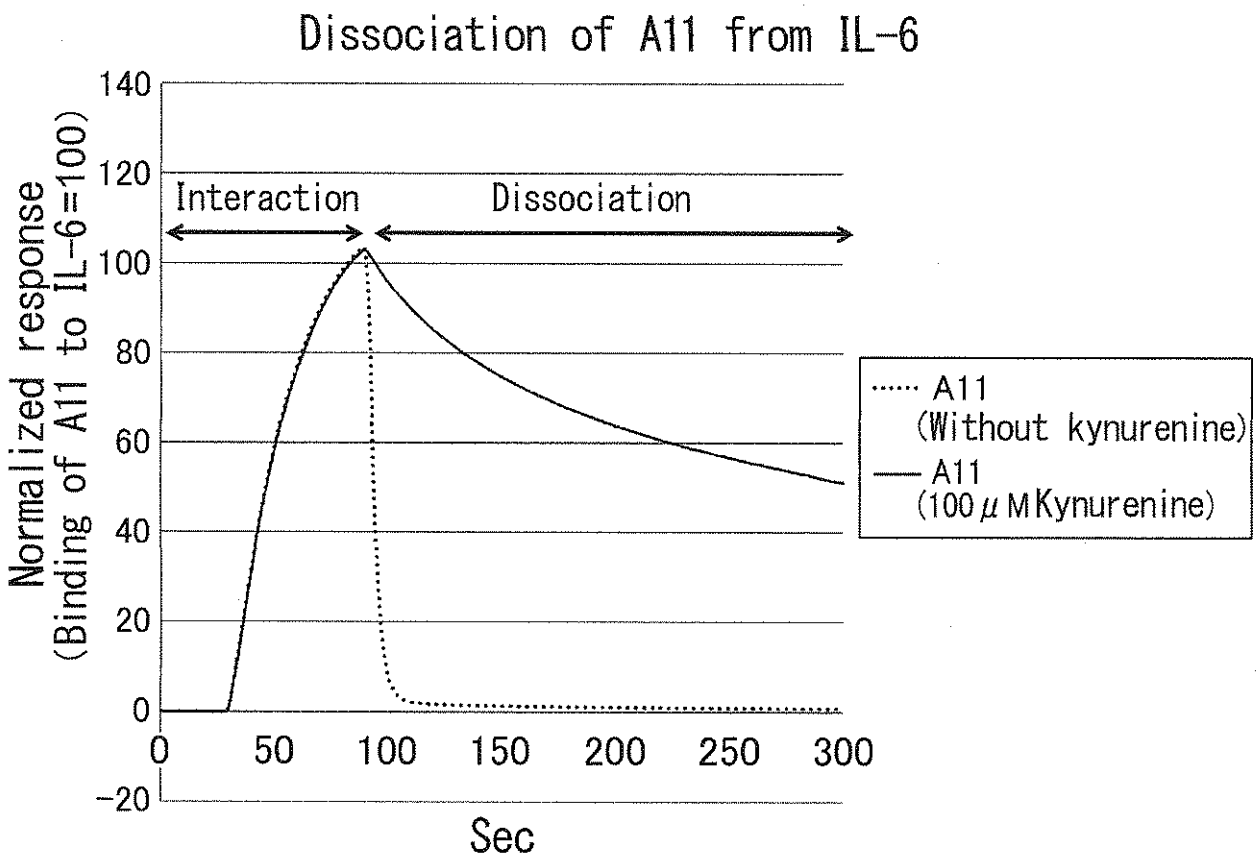

Dissociation of A11 from IL-6
Normalized response
(Binding of A11 to IL-6=100)
140
120
100
80
60
40
20
0
-20
0
50
100
150
200
250
300
Sec
Interaction
Dissociation
A11
(Without kynurenine)
A11
(100μMKynurenine)

Fig. 8

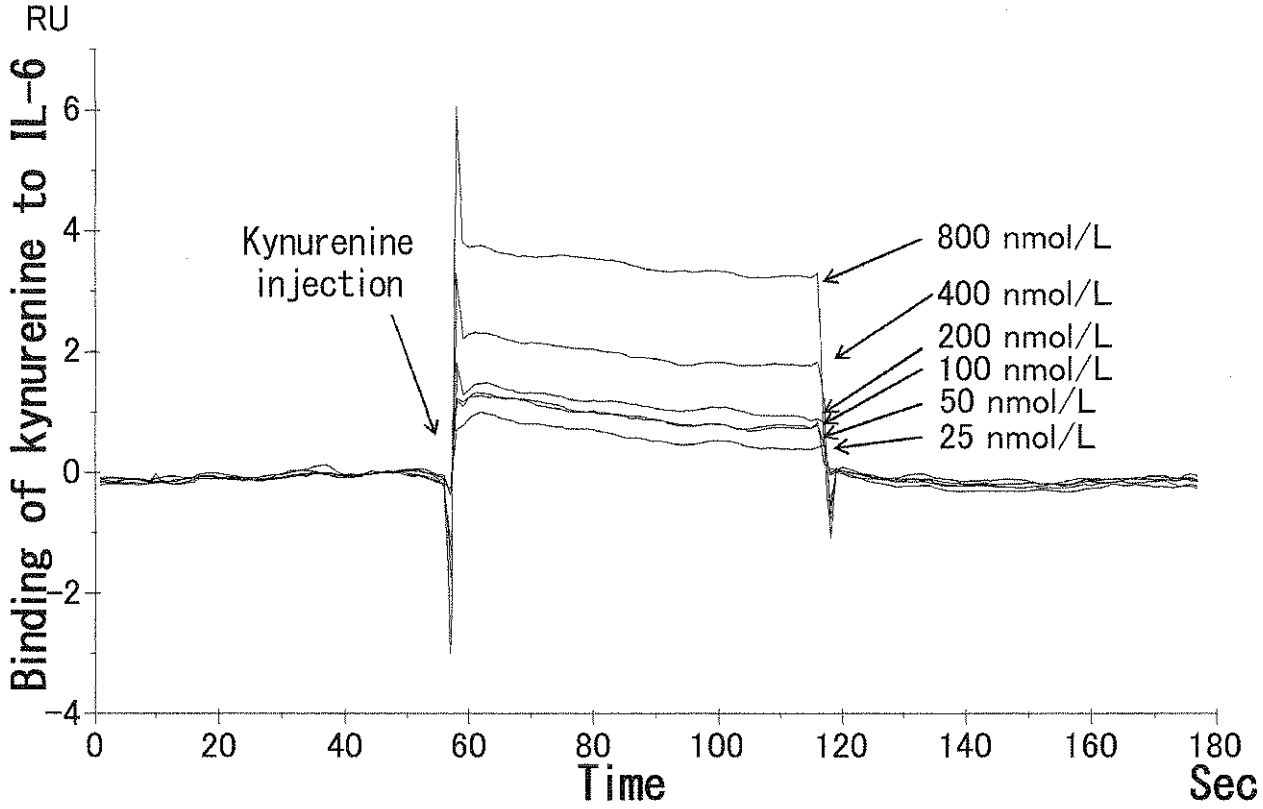

RU
Binding of Kynurenine to IL-6
6
4
2
0
−2
−4
Kynurenine
injection
800 nmol/L
400 nmol/L
200 nmol/L
100 nmol/L
50 nmol/L
25 nmol/L
0
20
40
60
80
100
120
140
160
180
Time
Sec

Fig. 9

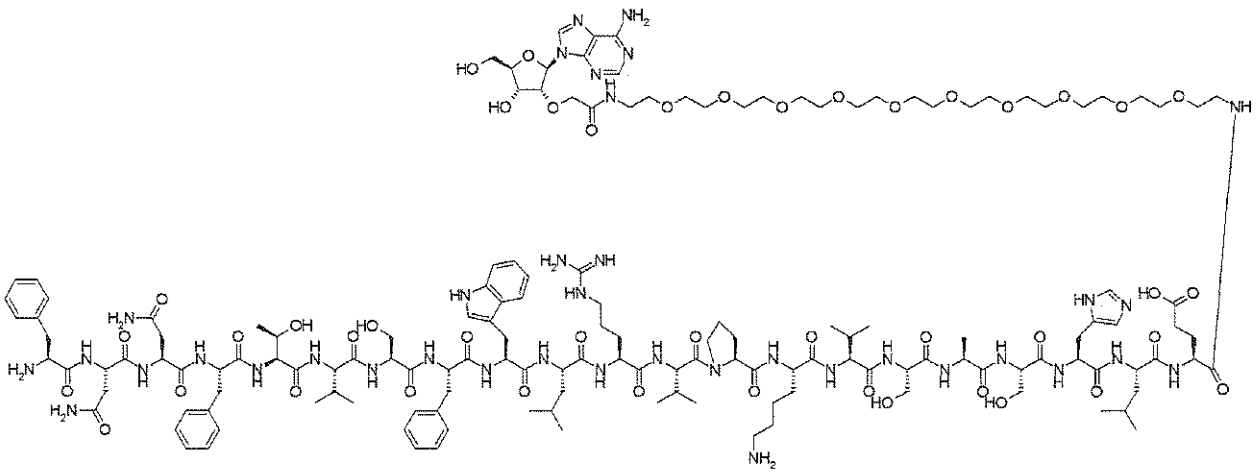


Fig. 10

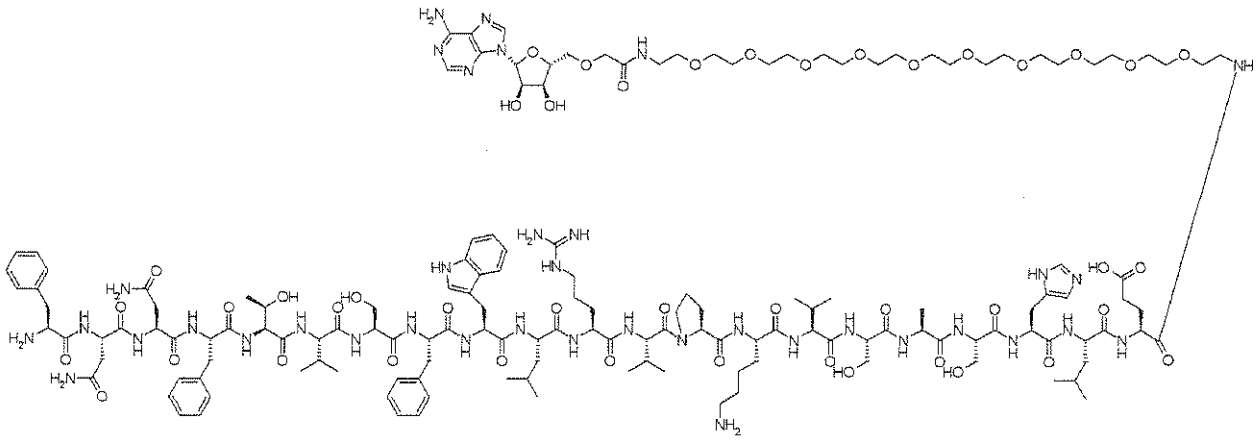


Fig. 11

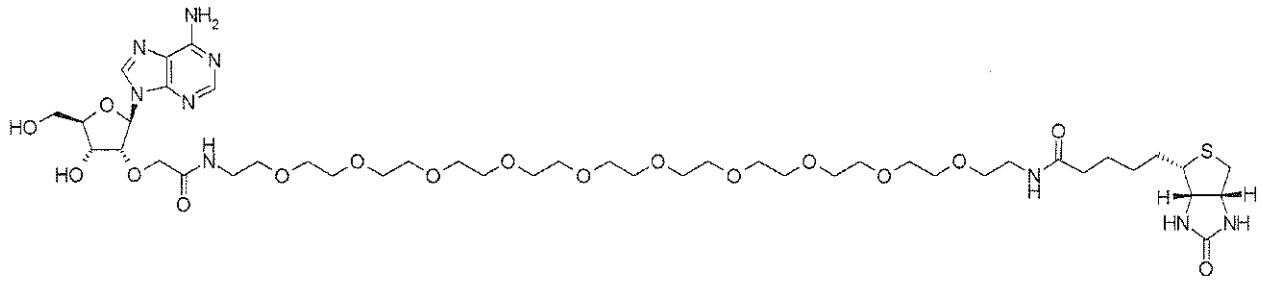


Fig. 12

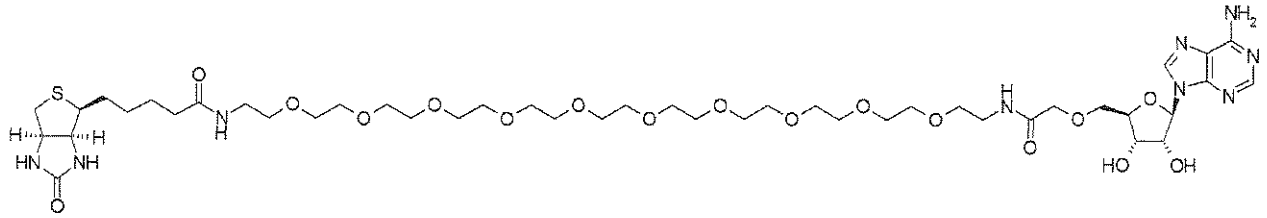


Fig. 13

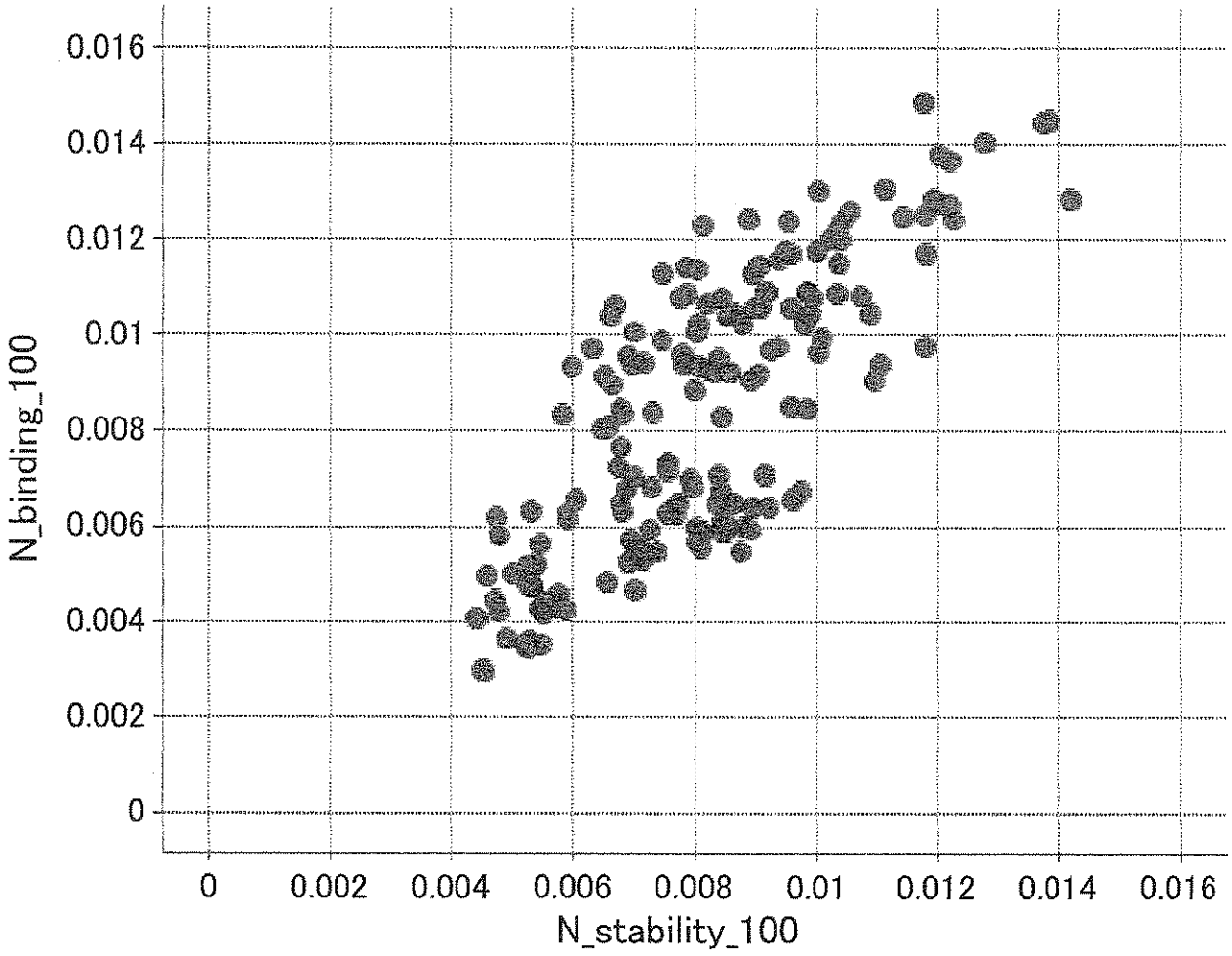

0.016
0.014
0.012
0.01
0.008
0.006
0.004
0.002
0
N_binding_100
0
0.002
0.004
0.006
0.008
0.01
0.012
0.014
0.016
N_stability_100

Fig. 14

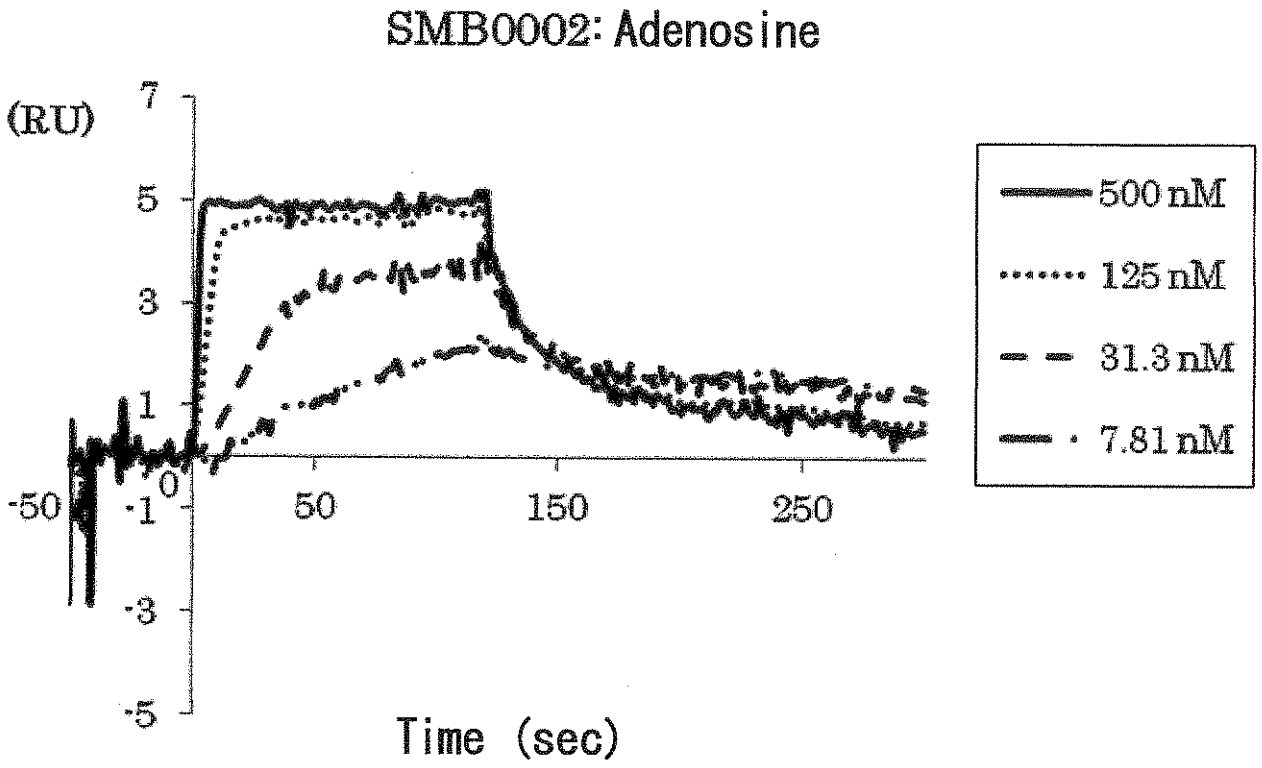

SMB0002: Adenosine
(RU)
7
5
3
1
-1
-3
-5
-50
0
50
150
250
Time (sec)
500 nM
125 nM
31.3 nM
7.81 nM

Fig. 15A

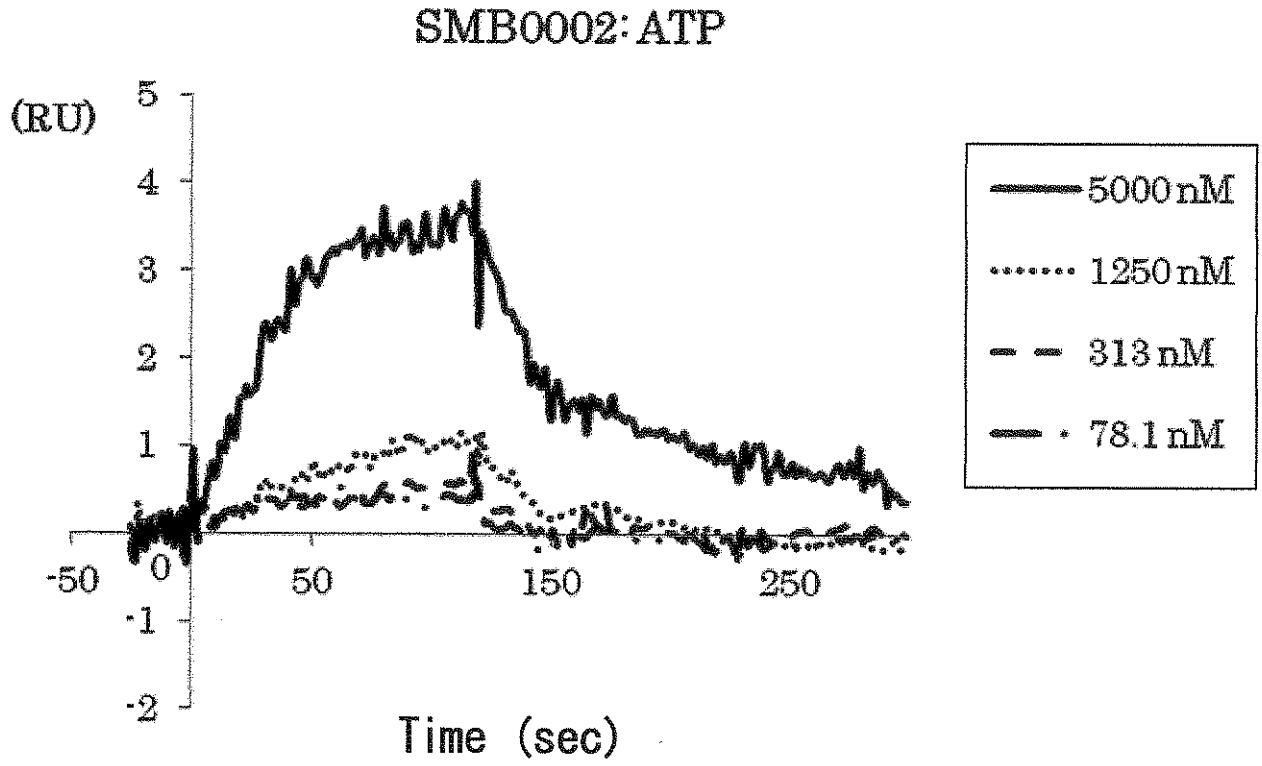

SMB0002: ATP
(RU)
5
4
3
2
1
-1
-2
-50
0
50
150
250
Time (sec)
5000 nM
1250 nM
313 nM
78.1 nM

Fig. 15B

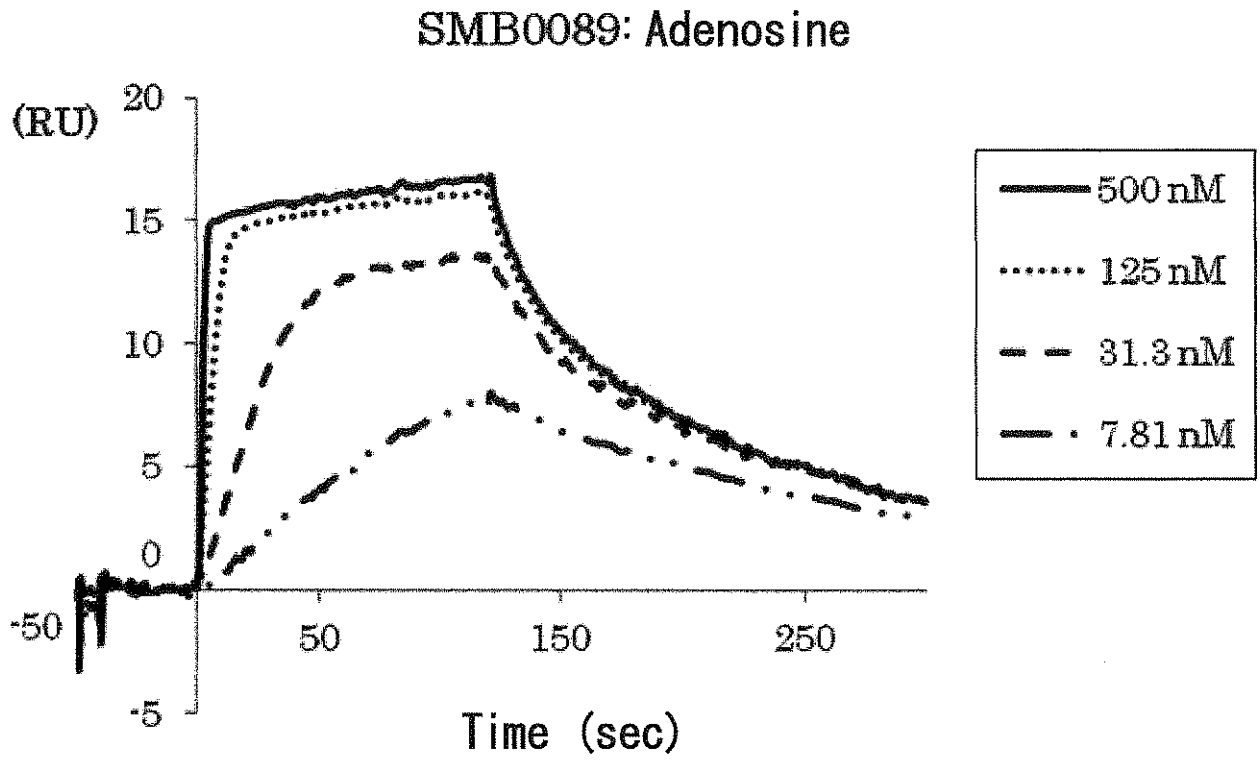

SMB0089: Adenosine
(RU)
20
15
10
5
0
-5
-50
50
150
250
Time (sec)
500 nM
125 nM
31.3 nM
7.81 nM

Fig. 15C

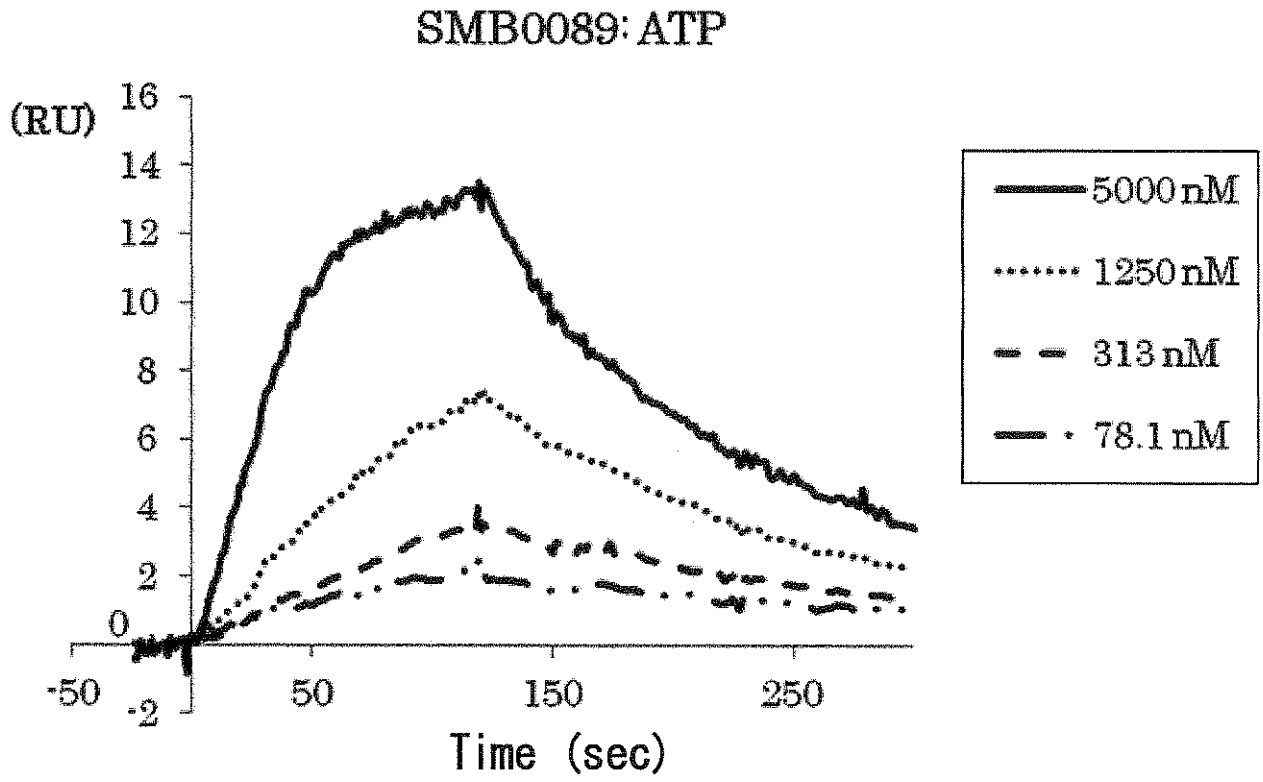

SMB0089: ATP
(RU)
16
14
12
10
8
6
4
2
0
-2
-50
50
150
250
Time (sec)
5000 nM
1250 nM
313 nM
78.1 nM

Fig. 15D

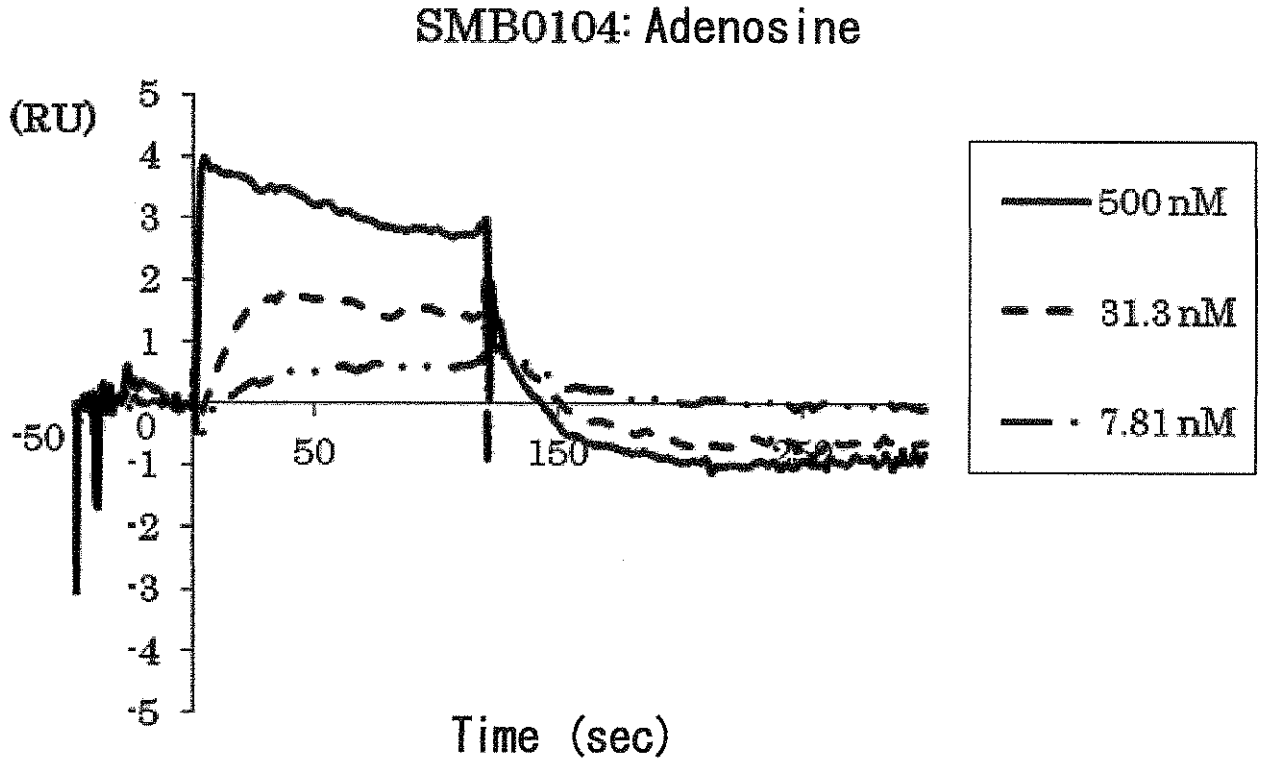

SMB0104: Adenosine
(RU)
5
4
3
2
1
0
-1
-2
-3
-4
-5
-50
50
150
500 nM
31.3 nM
7.81 nM
Time (sec)

Fig. 15E

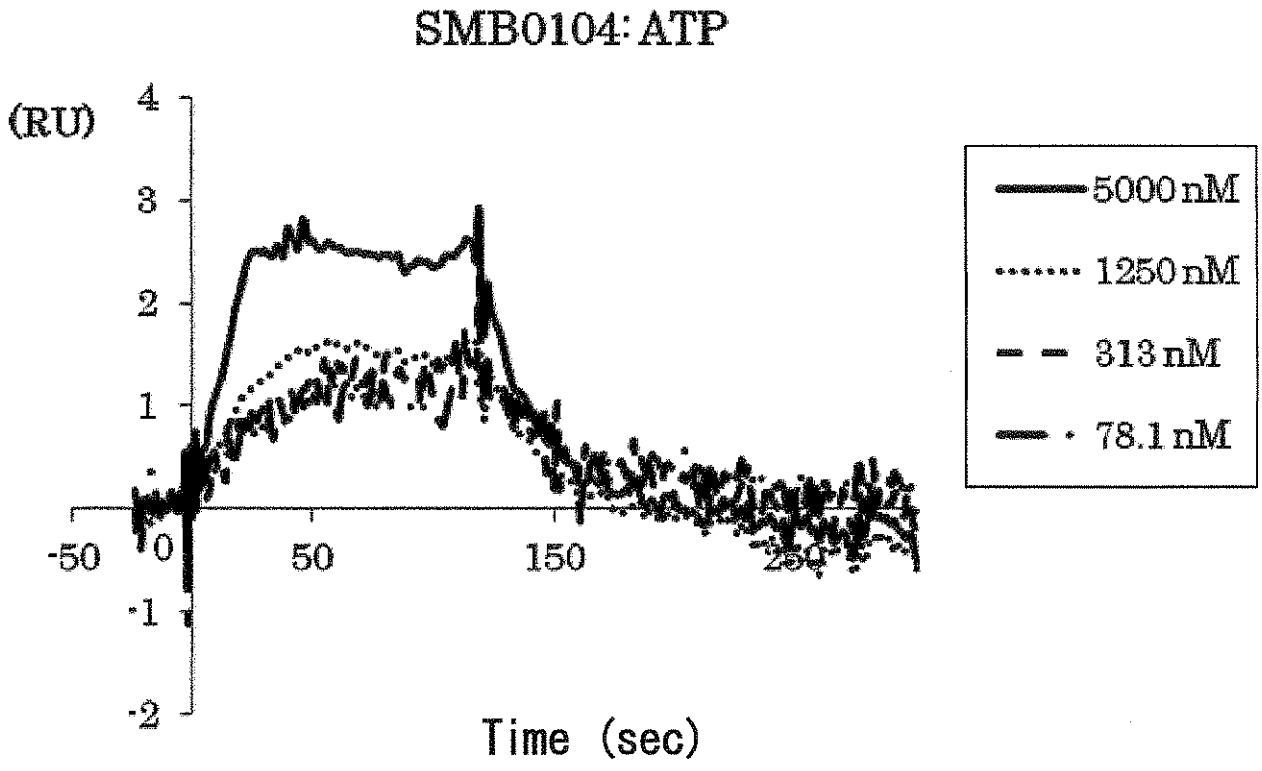

SMB0104: ATP
(RU)
4
3
2
1
-1
-2
-50
0
50
150
250
Time (sec)
5000 nM
1250 nM
313 nM
78.1 nM

Fig. 15F

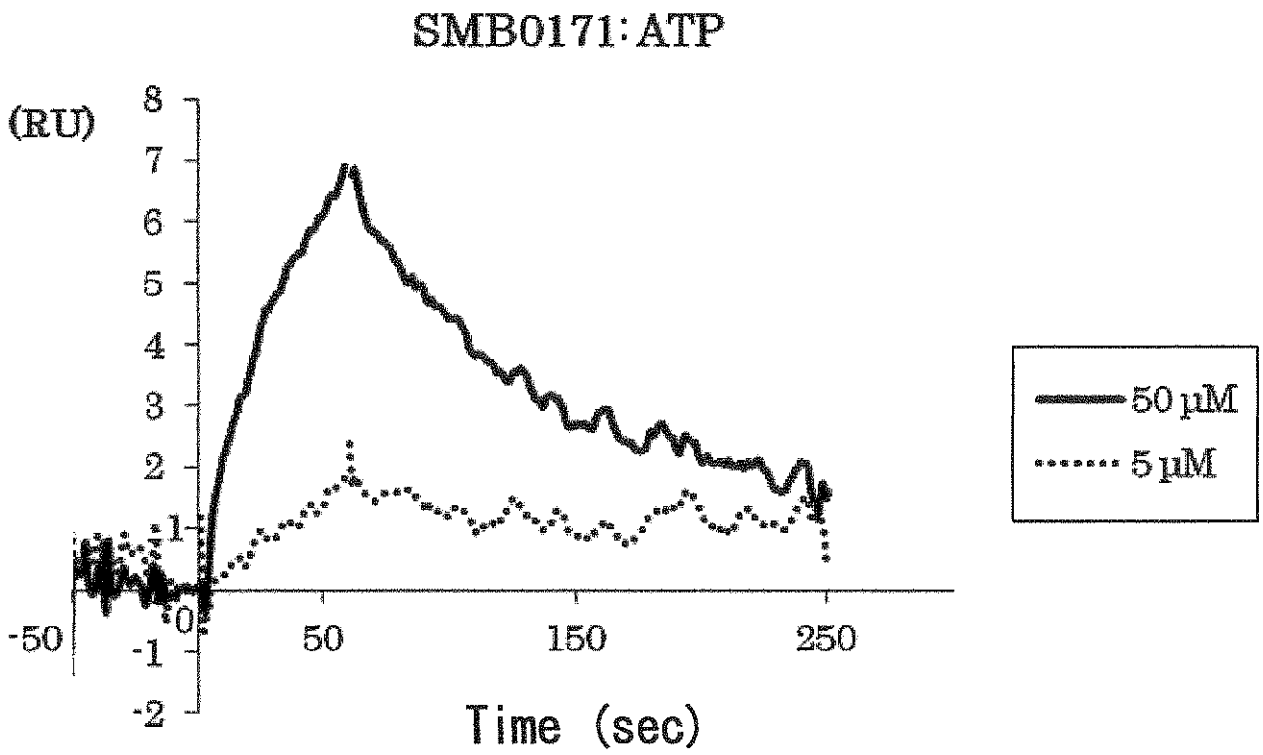


Fig. 16

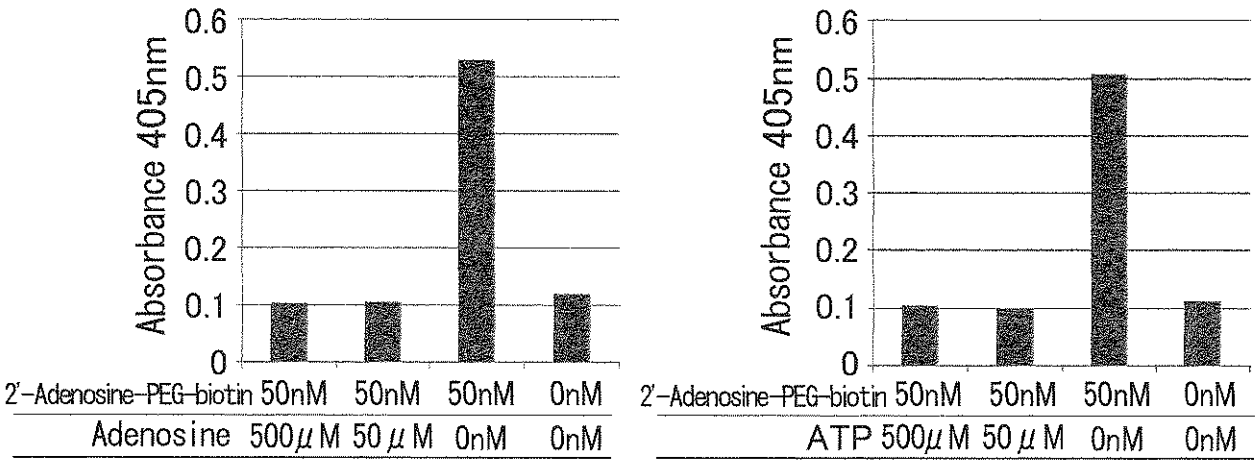

Absorbance 405nm
0.6
0.5
0.4
0.3
0.2
0.1
0
2'-Adenosine-PEG-biotin 50nM 50nM 50nM 0nM
Adenosine 500μM 50μM 0nM 0nM
Absorbance 405nm
0.6
0.5
0.4
0.3
0.2
0.1
0
2'-Adenosine-PEG-biotin 50nM 50nM 50nM 0nM
ATP 500μM 50μM 0nM 0nM

Fig. 17

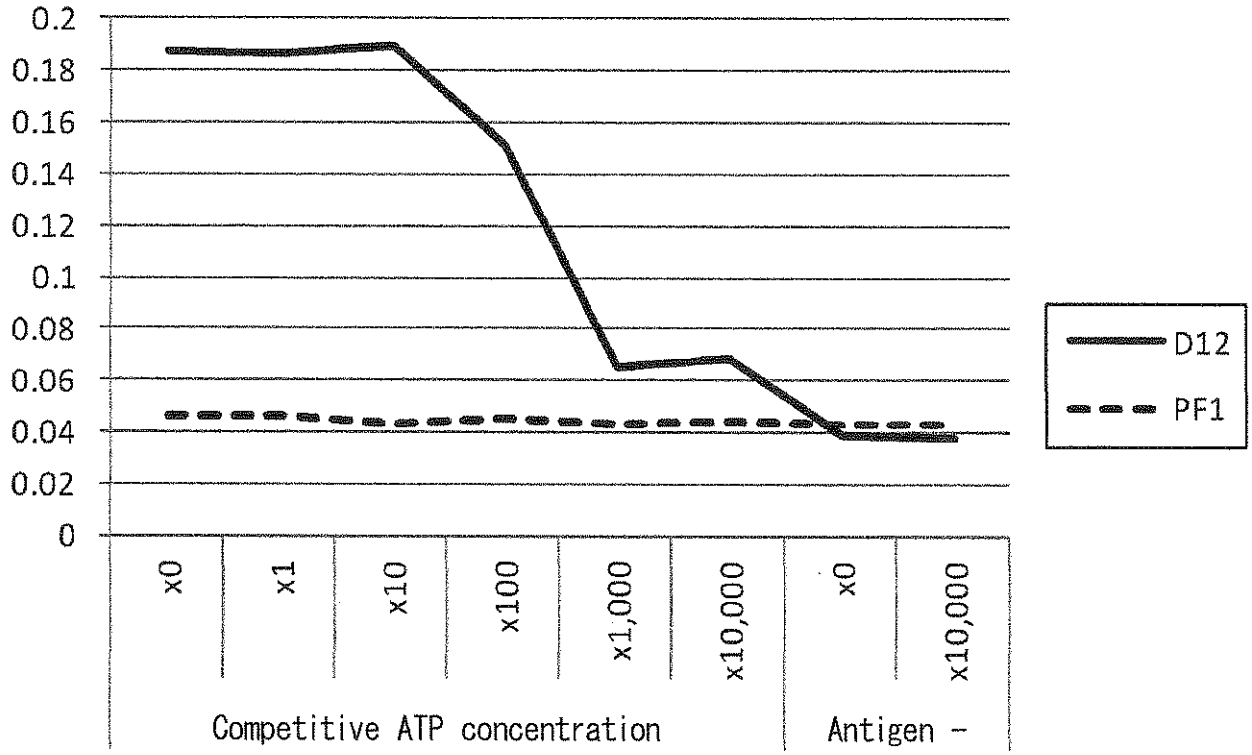

0.2
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
x0
x1
x10
x100
x1,000
x10,000
x0
x10,000
Competitive ATP concentration
Antigen -
D12
PF1

Fig. 18

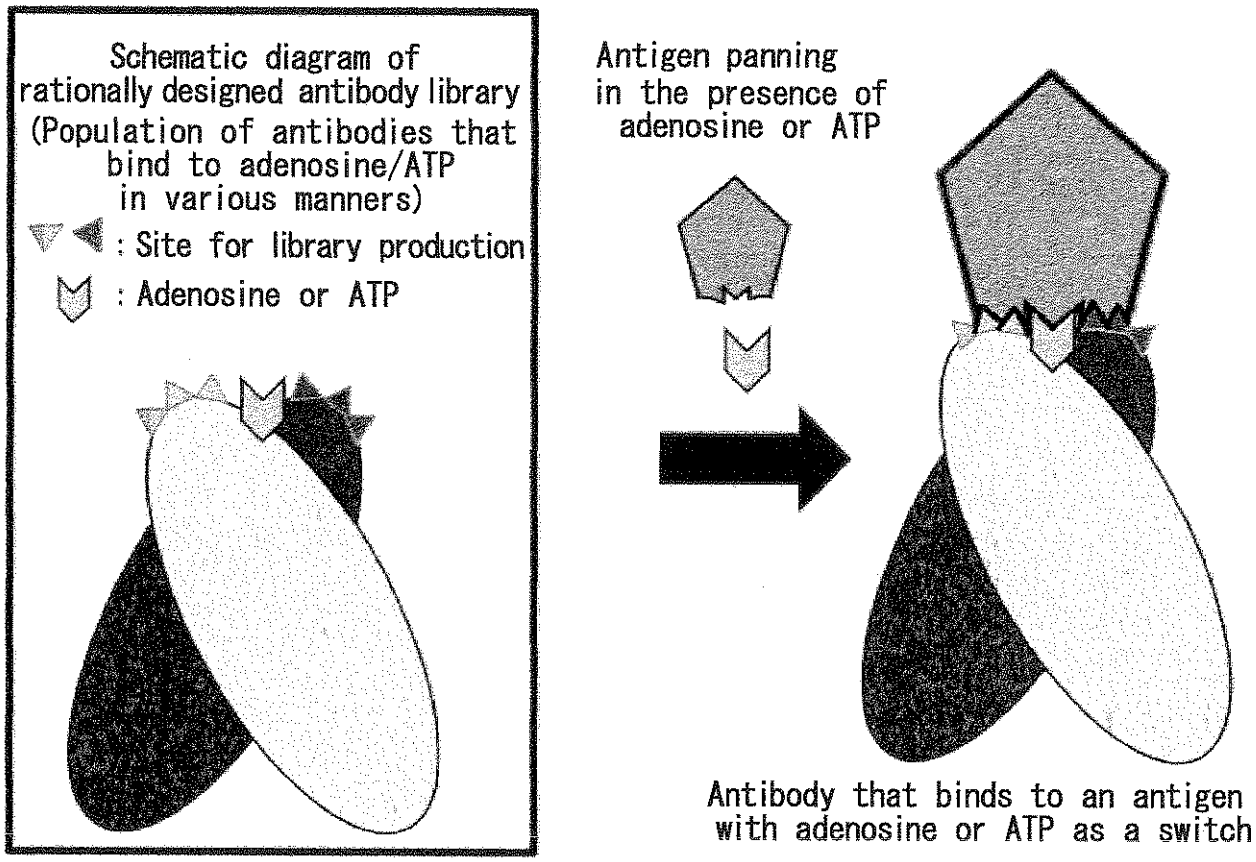

Schematic diagram of
rationally designed antibody library
(Population of antibodies that
bind to adenosine/ATP
in various manners)
: Site for library production
: Adenosine or ATP
Antigen panning
in the presence of
adenosine or ATP
Antibody that binds to an antigen
with adenosine or ATP as a switch

Fig. 19

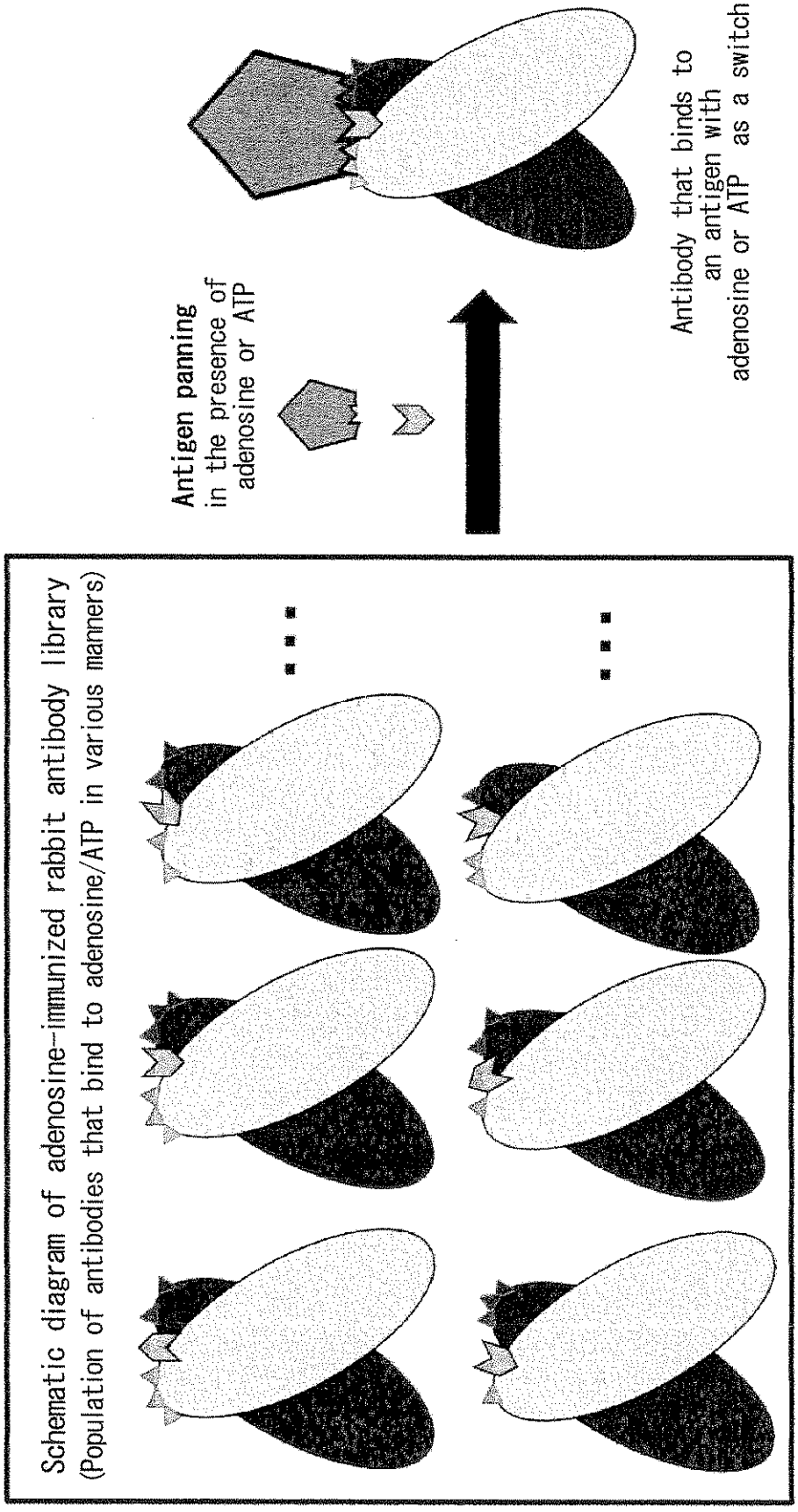

Schematic diagram of adenosine-immunized rabbit antibody library
(Population of antibodies that bind to adenosine/ATP in various manners)
Antigen panning
in the presence of
adenosine or ATP
Antibody that binds to
an antigen with
adenosine or ATP as a switch

FIG. 20

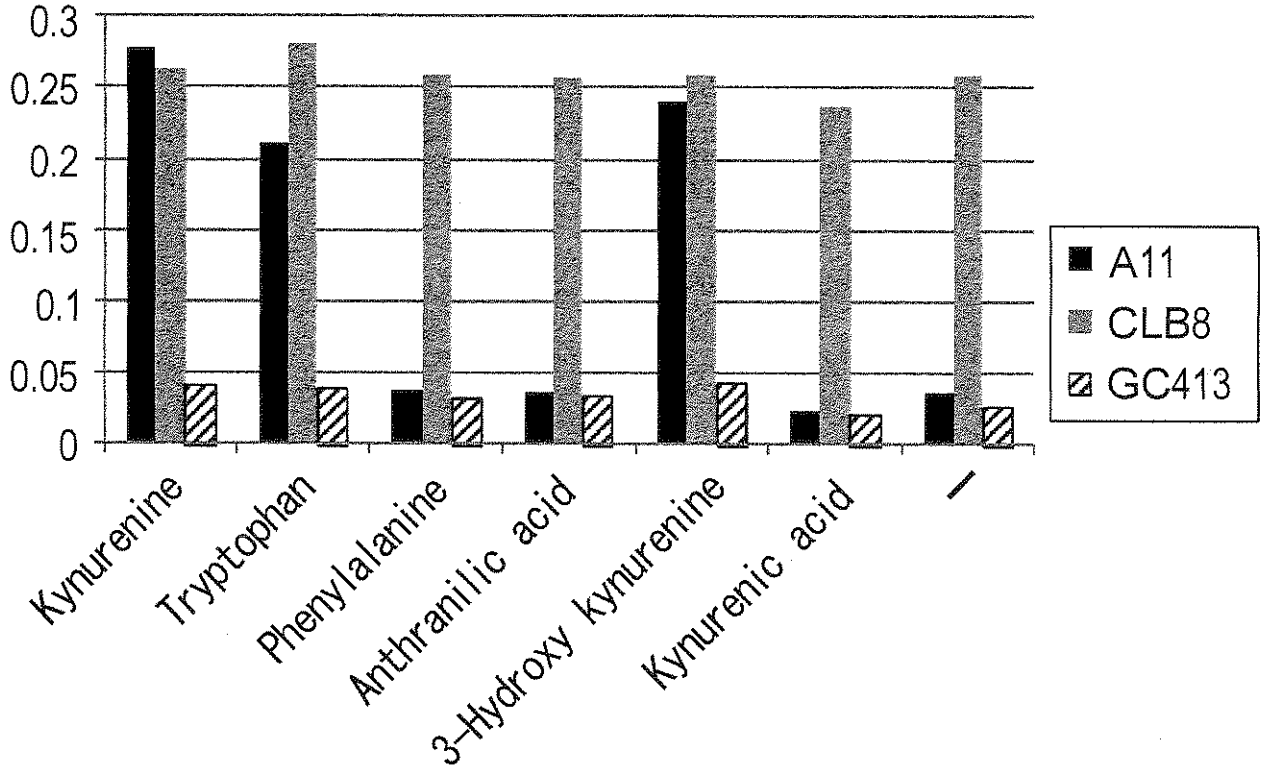

0.3
0.25
0.2
0.15
0.1
0.05
0
A11
CLB8
GC413
Kynurenine
Tryptophan
Phenylalanine
Anthranilic acid
3-Hydroxy kynurenine
Kynurenic acid
—

Fig. 21

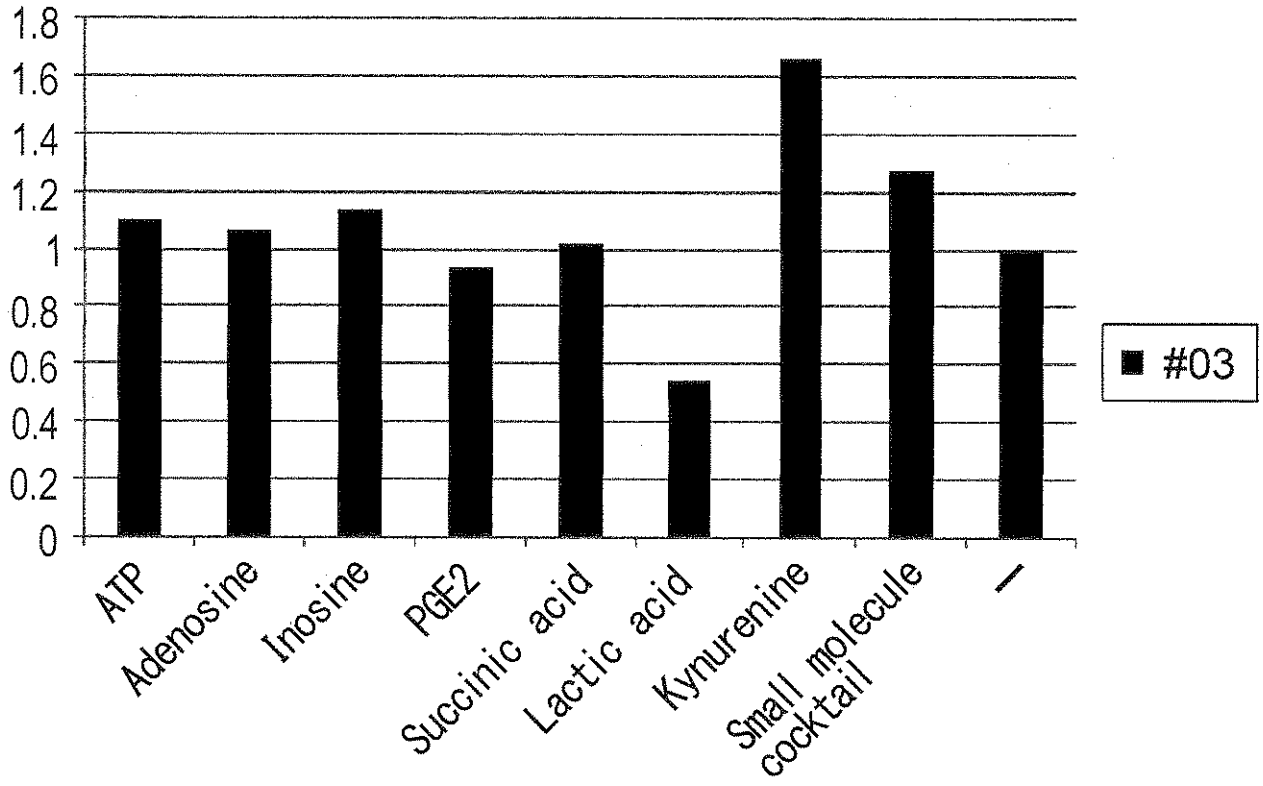

1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
ATP
Adenosine
Inosine
PGE2
Succinic acid
Lactic acid
Kynurenine
Small molecule cocktail
—
#03

Fig. 22

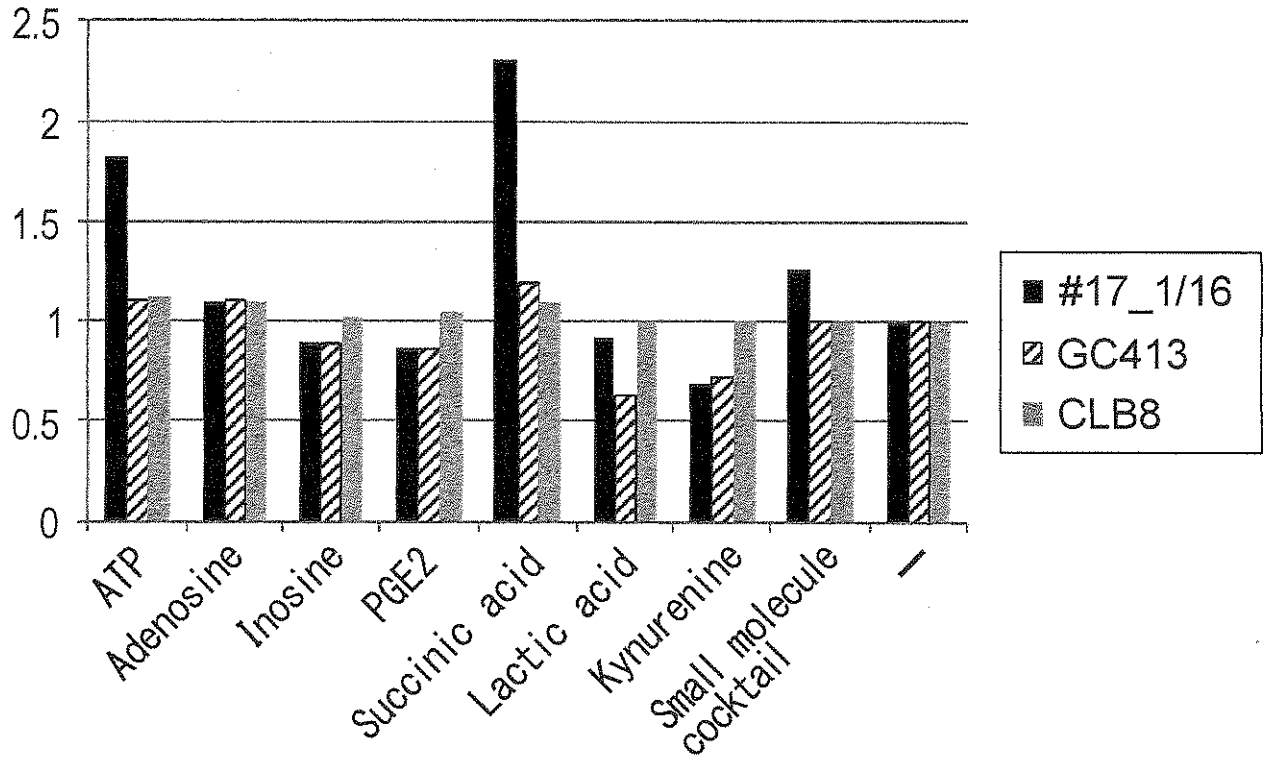

2.5
2
1.5
1
0.5
0
ATP
Adenosine
Inosine
PGE2
Succinic acid
Lactic acid
Kynurenine
Small molecule cocktail
—
#17_1/16
GC413
CLB8

Fig. 23

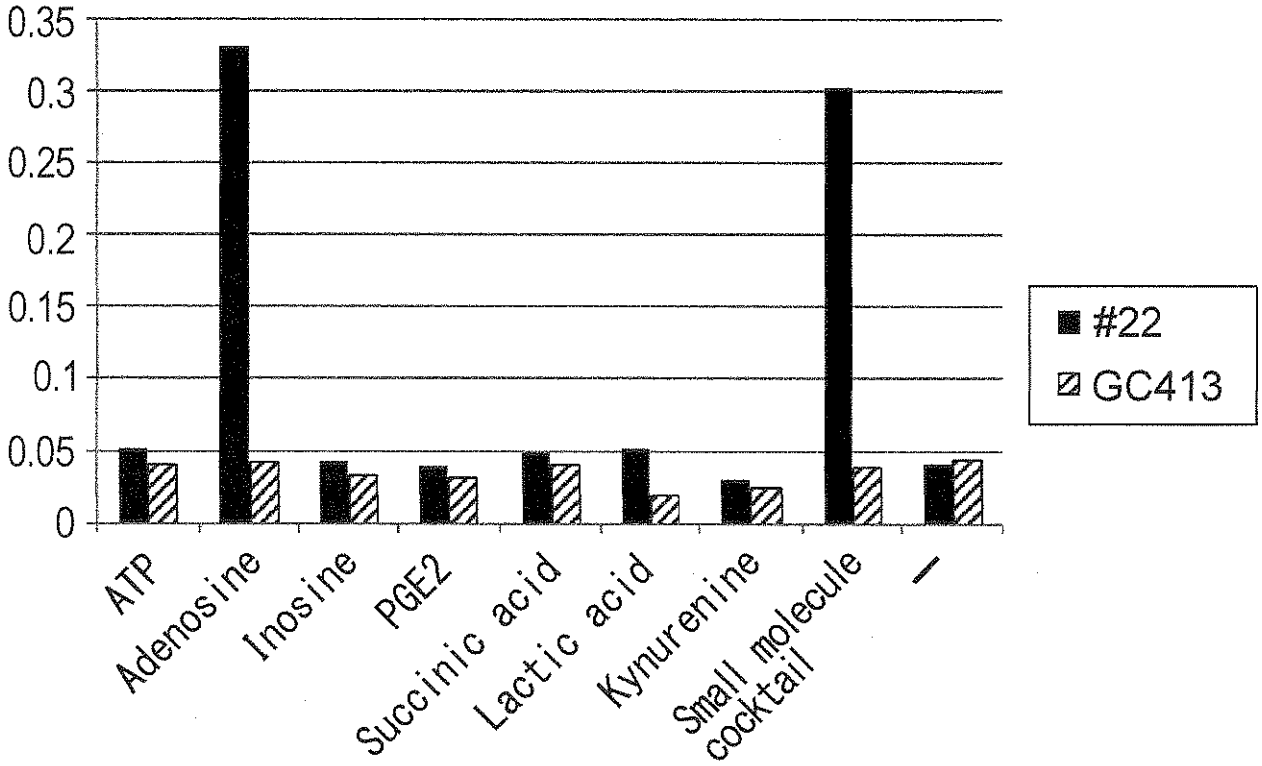

0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
ATP
Adenosine
Inosine
PGE2
Succinic acid
Lactic acid
Kynurenine
Small molecule cocktail
—
#22
GC413

Fig. 24

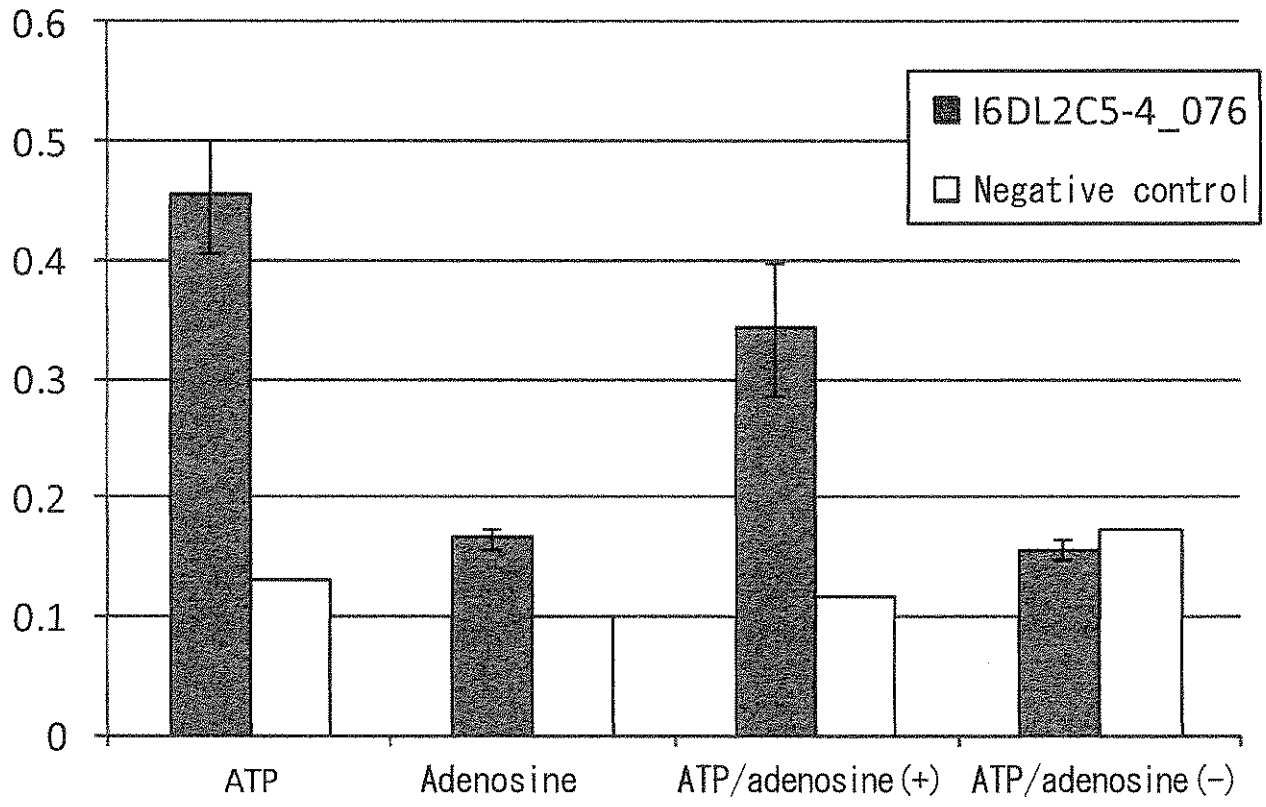

0.6
0.5
0.4
0.3
0.2
0.1
0
I6DL2C5-4_076
Negative control
ATP
Adenosine
ATP/adenosine (+)
ATP/adenosine (−)

Fig. 25

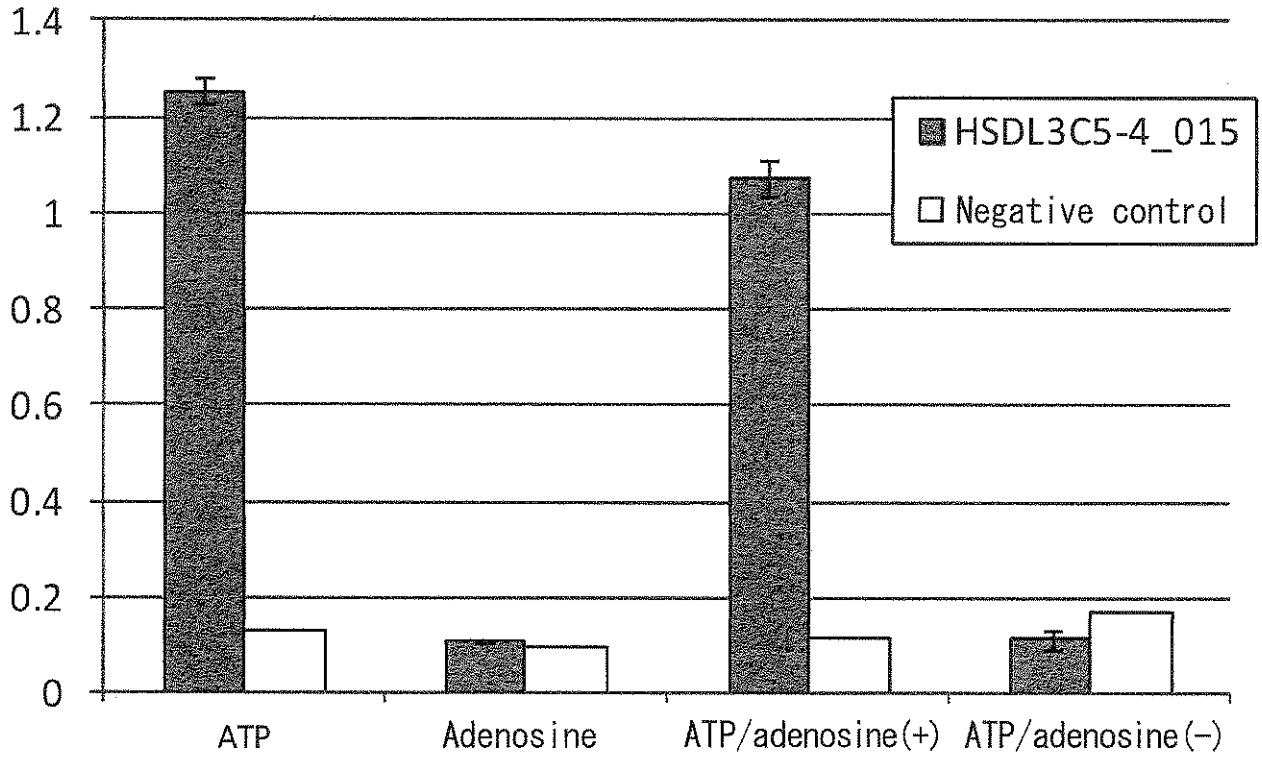

1.4
1.2
1
0.8
0.6
0.4
0.2
0
HSDL3C5-4_015
Negative control
ATP
Adenosine
ATP/adenosine(+)
ATP/adenosine(−)

Fig. 26

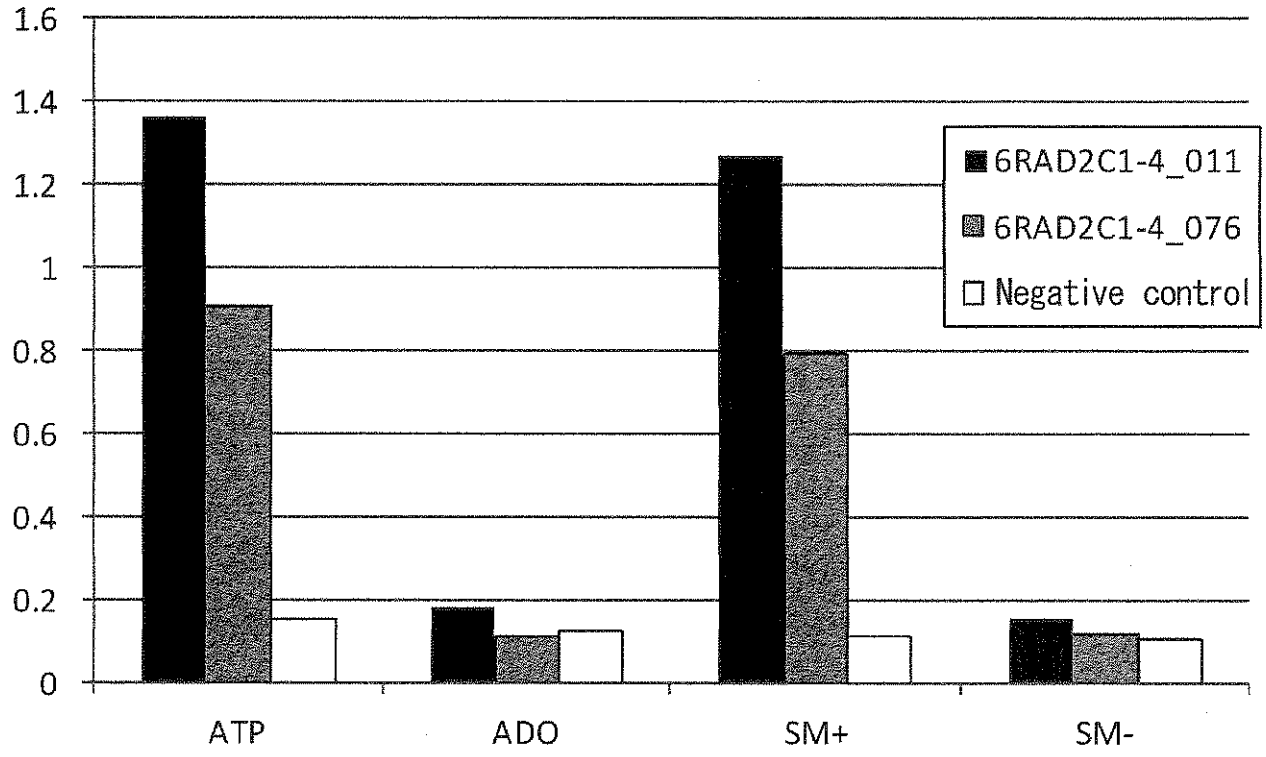

1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
ATP
ADO
SM+
SM-
6RAD2C1-4_011
6RAD2C1-4_076
Negative control

Fig. 27

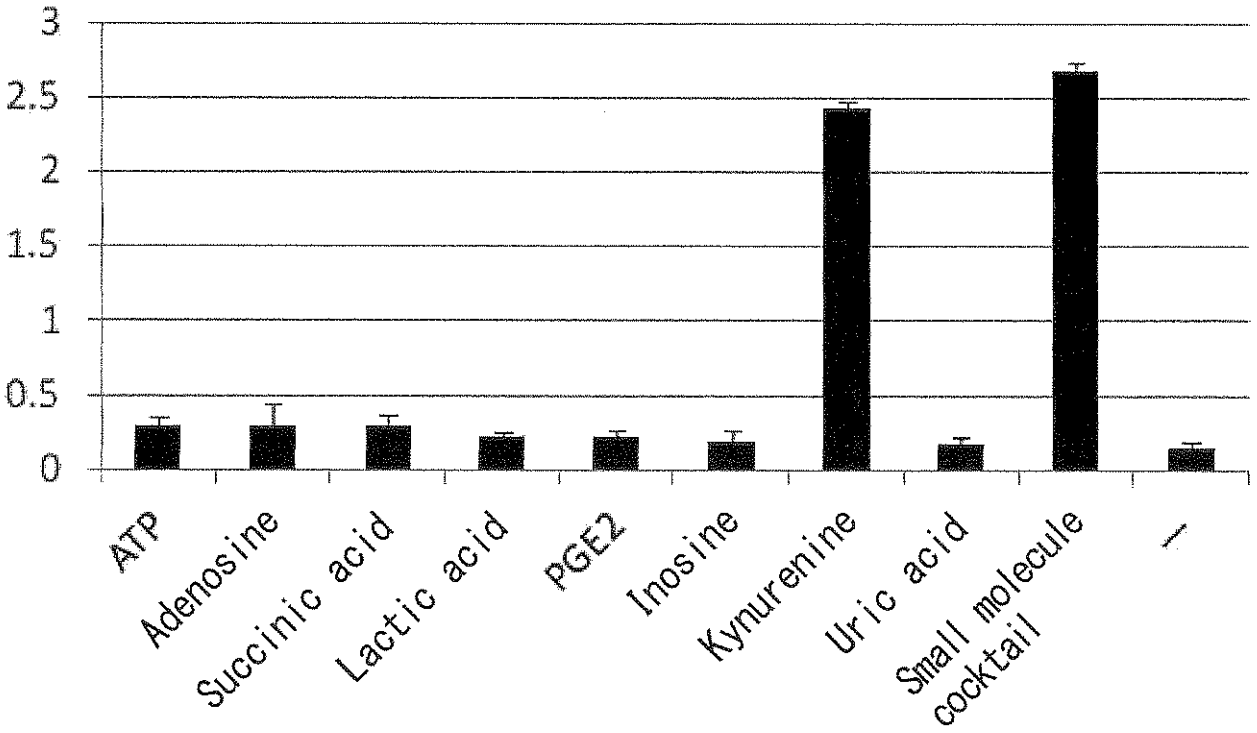

3
2.5
2
1.5
1
0.5
0
ATP
Adenosine
Succinic acid
Lactic acid
PGE2
Inosine
Kynurenine
Uric acid
Small molecule cocktail
—

Fig. 28

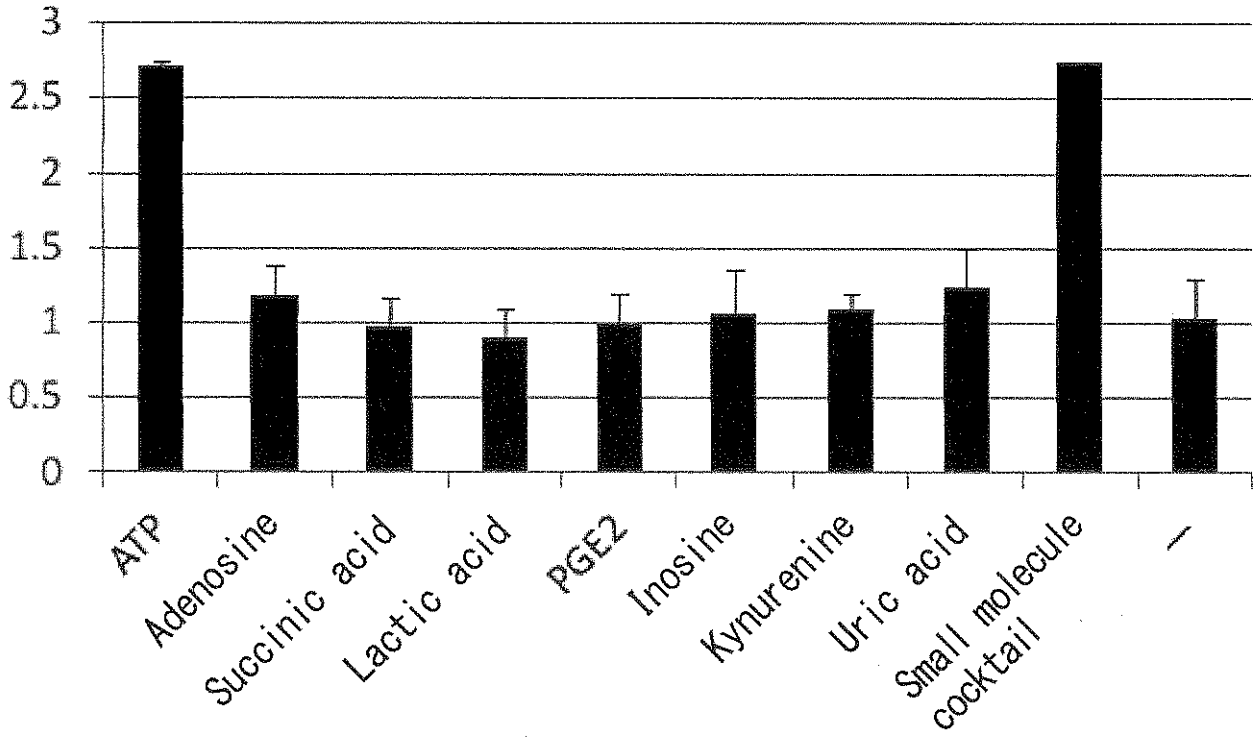

3
2.5
2
1.5
1
0.5
0
ATP
Adenosine
Succinic acid
Lactic acid
PGE2
Inosine
Kynurenine
Uric acid
Small molecule cocktail
–

Fig. 29

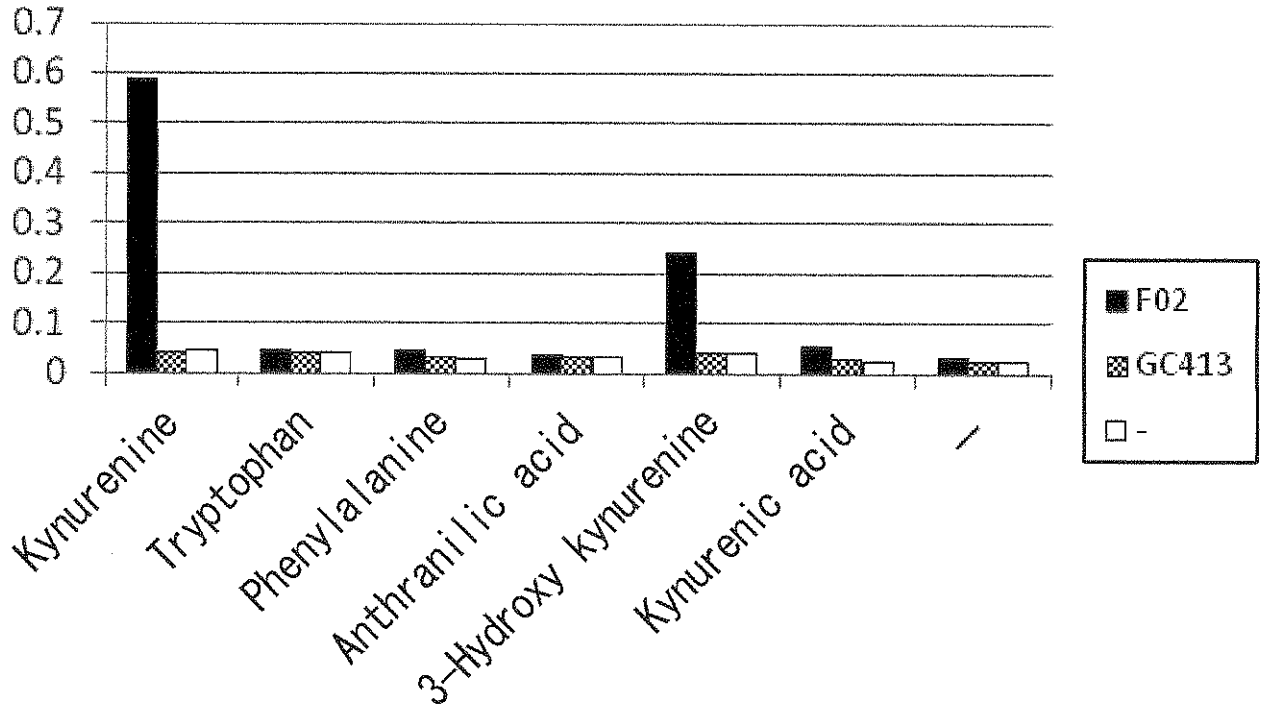

0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Kynurenine
Tryptophan
Phenylalanine
Anthranilic acid
3-Hydroxy kynurenine
Kynurenic acid
F02
GC413
-

Fig. 30

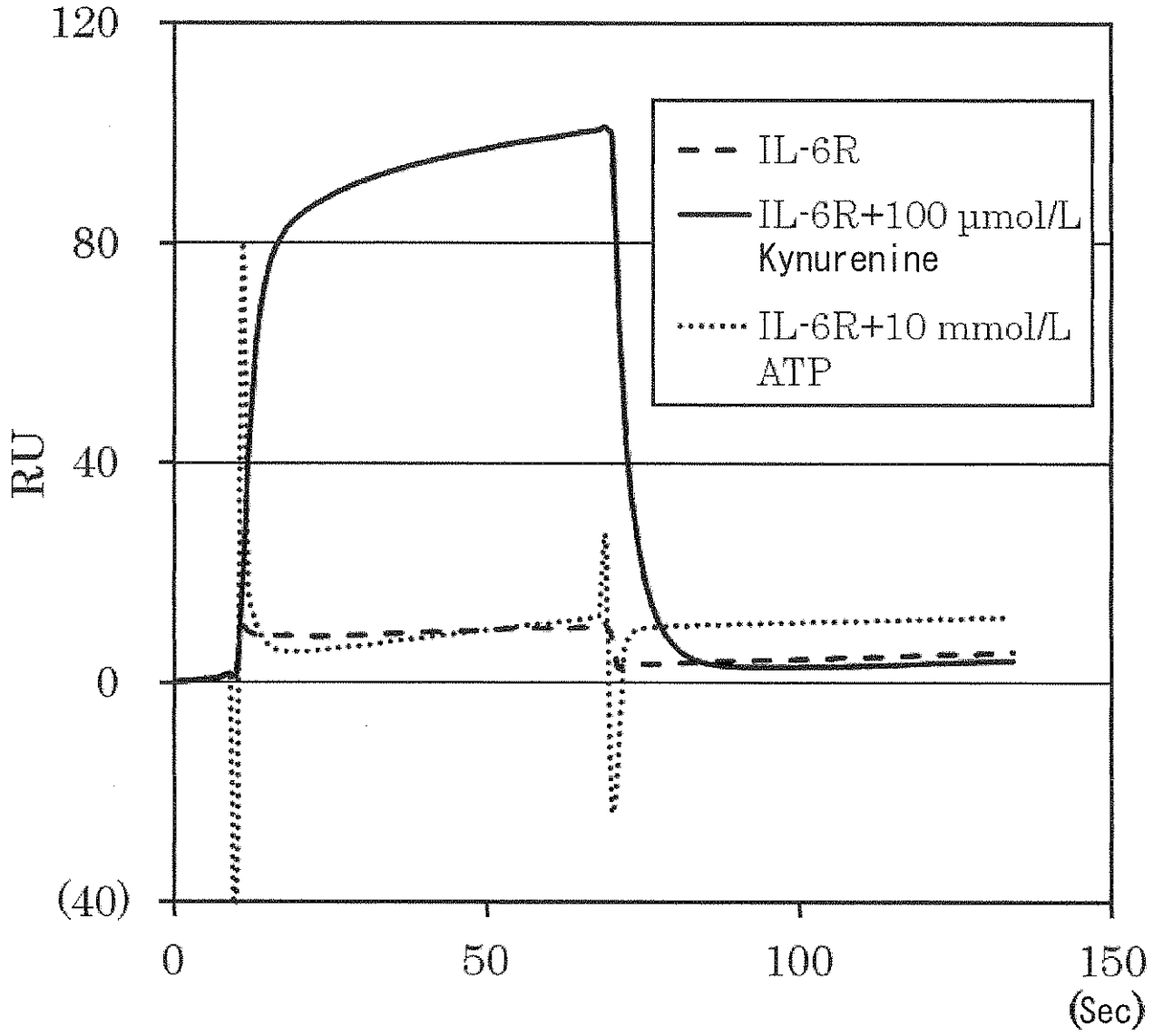

120
80
40
0
(40)
RU
0
50
100
150
(Sec)
IL-6R
IL-6R+100 μmol/L Kynurenine
IL-6R+10 mmol/L ATP

Fig. 31

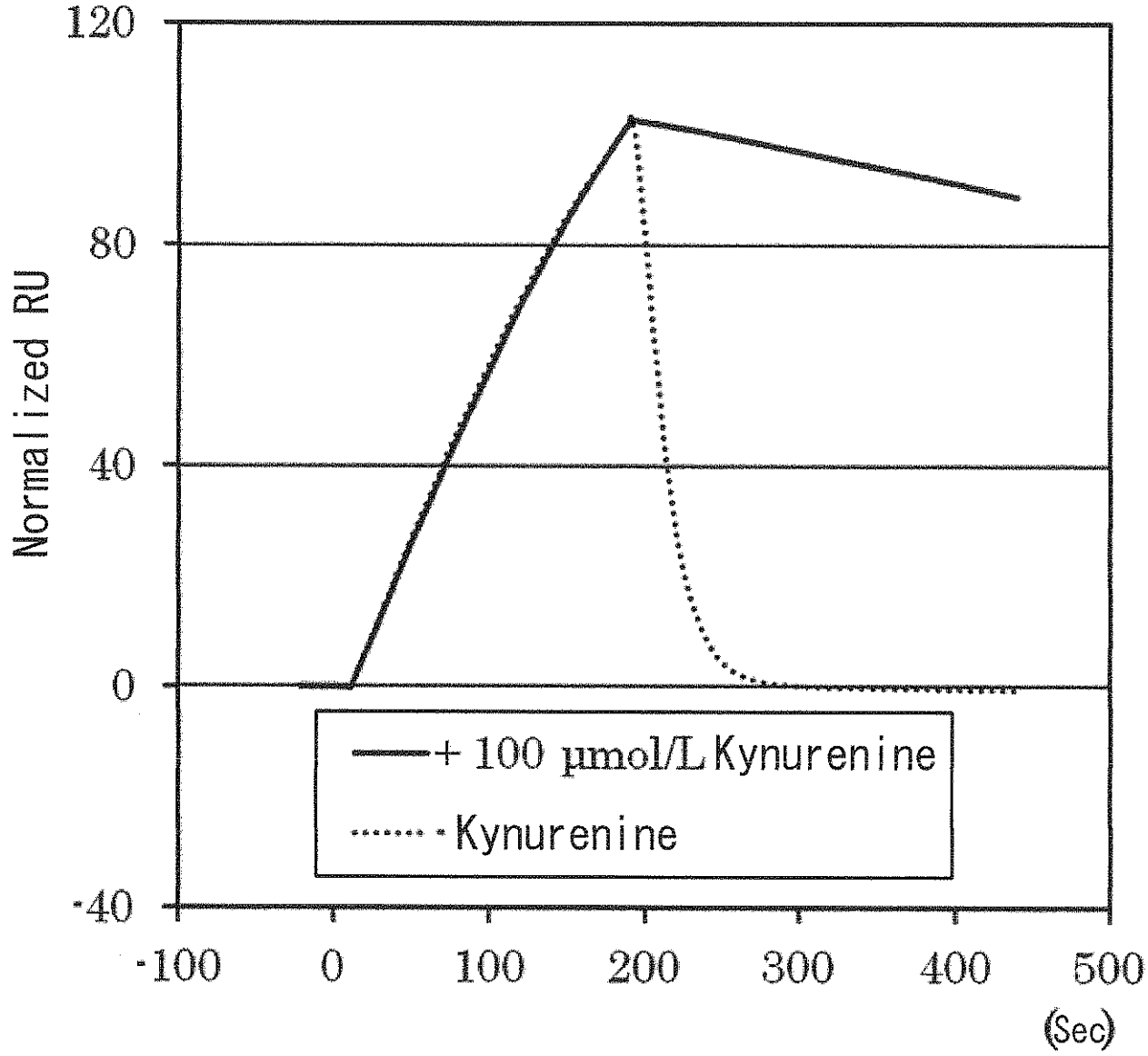

120
80
40
0
-40
Normalized RU
-100
0
100
200
300
400
500
(Sec)
+ 100 μmol/L Kynurenine
Kynurenine

Fig. 32

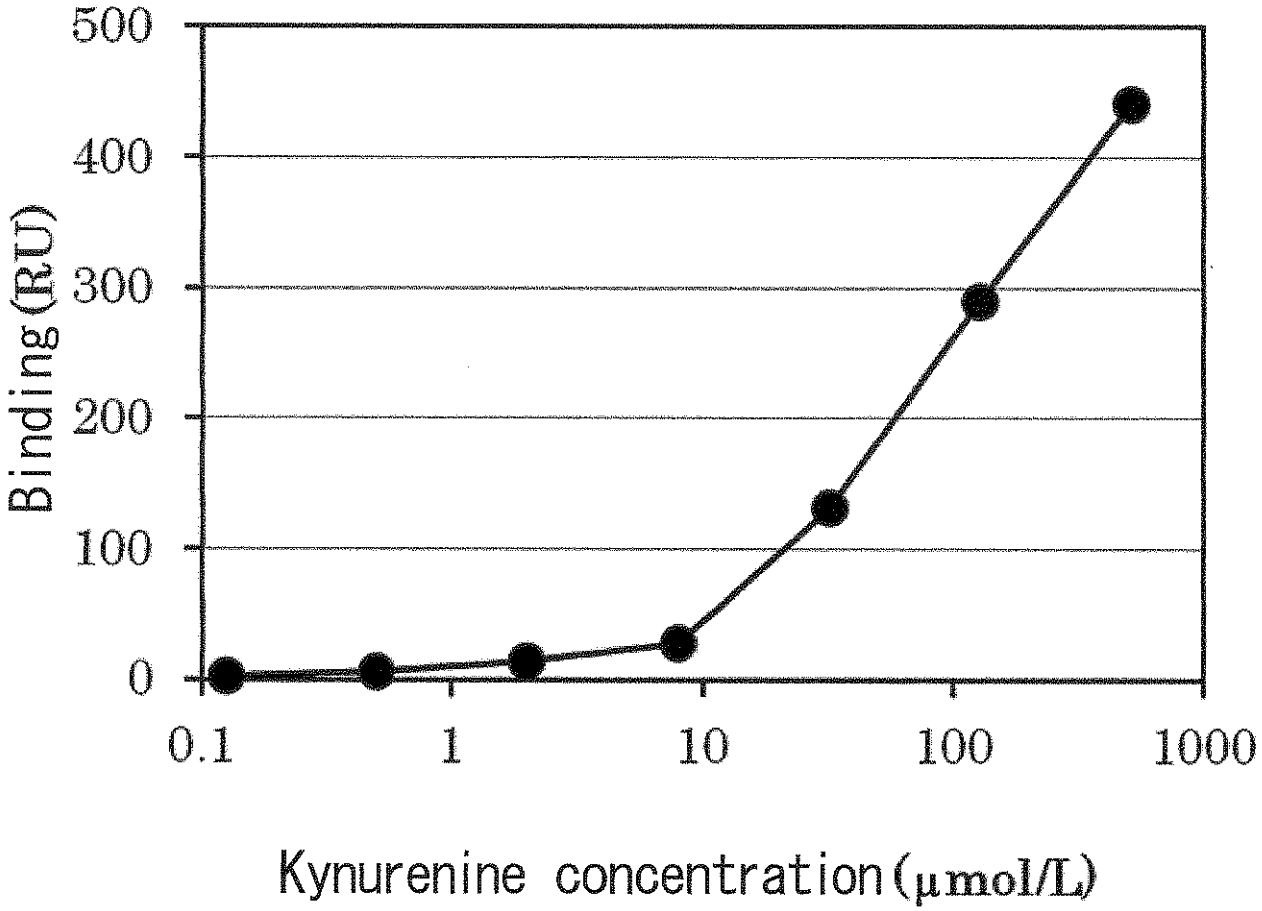

500
400
300
200
100
0
Binding(RU)
0.1
1
10
100
1000
Kynurenine concentration(μmol/L)

Fig. 33

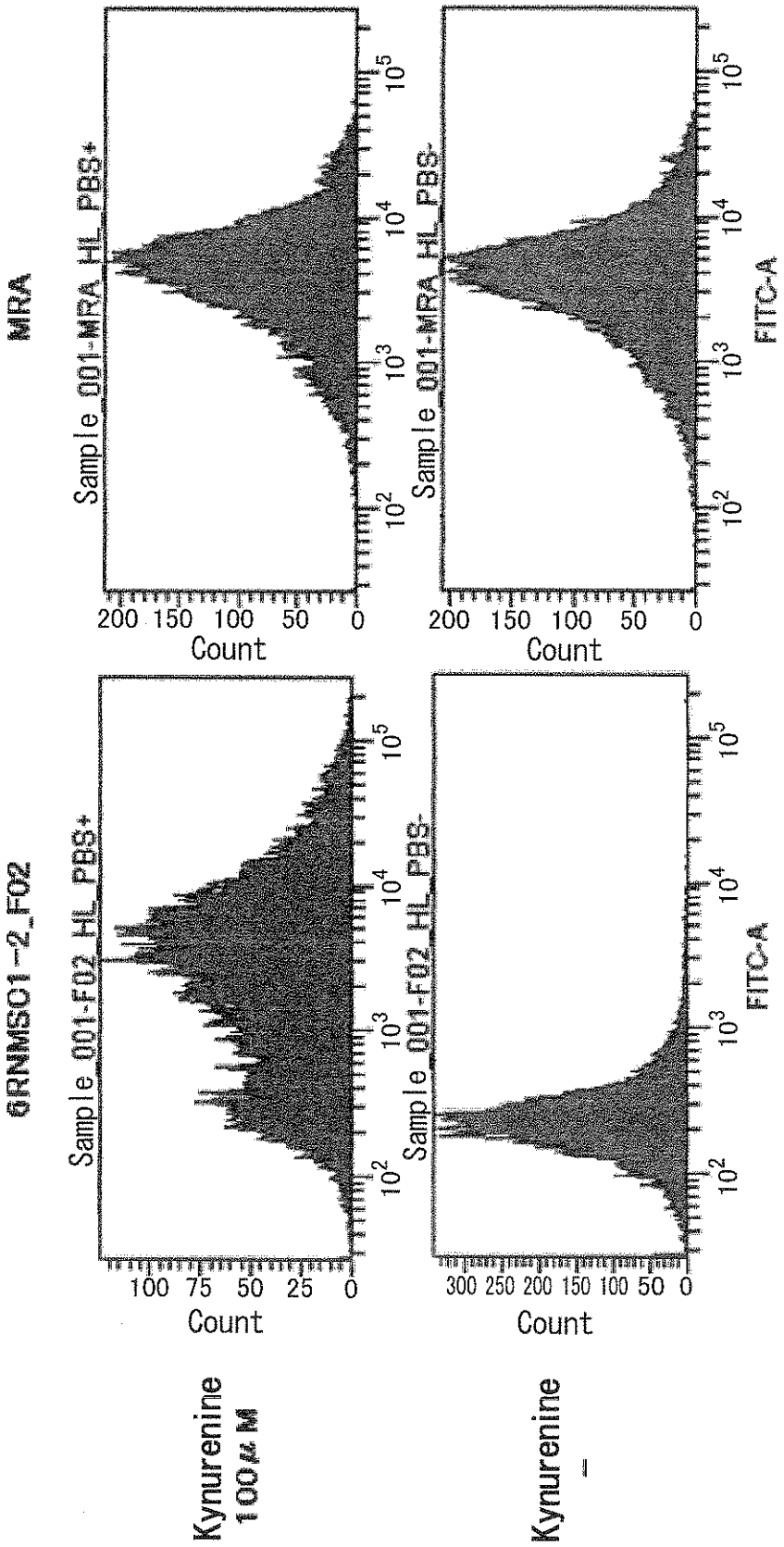

MRA
6RNMS01-2_F02
Sample_001-MRA_HL_PBS+
Sample_001-MRA_HL_PBS-
Sample_001-F02_HL_PBS+
Sample_001-F02_HL_PBS-
Count
FITC-A
Kynurenine 100μM
Kynurenine –

FIG. 34

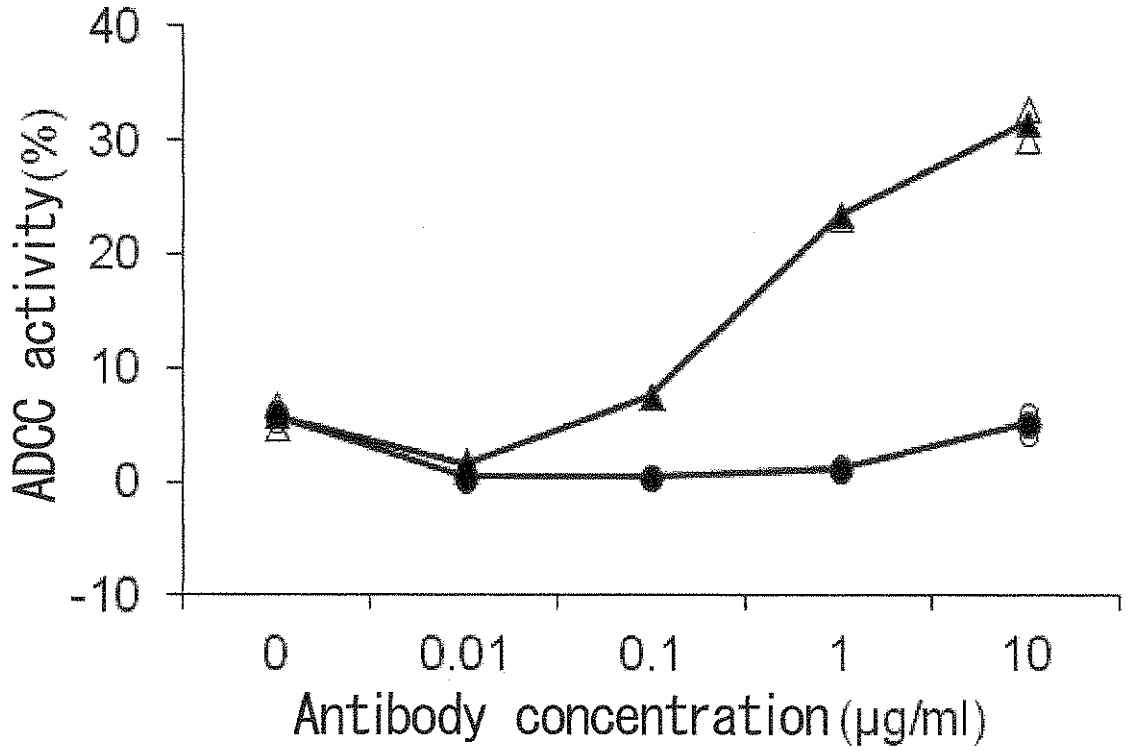

40
30
20
10
0
-10
ADCC activity(%)
0
0.01
0.1
1
10
Antibody concentration(μg/ml)

Fig. 35A

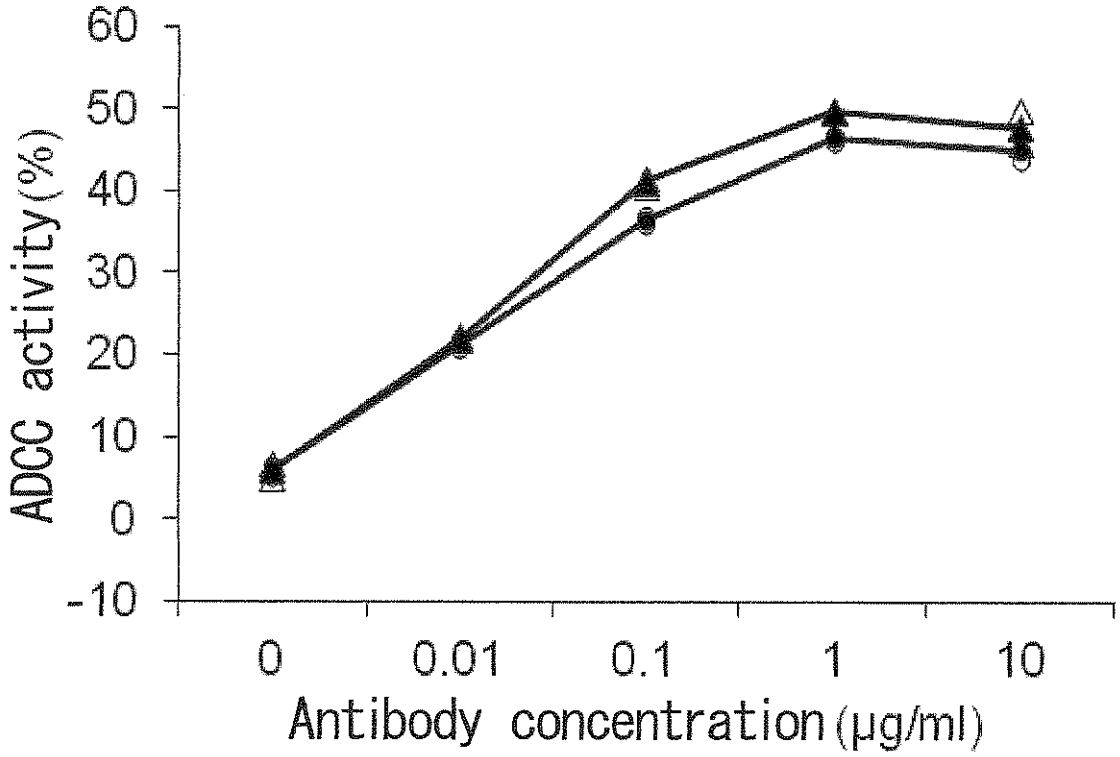

60
50
40
30
20
10
0
-10
ADCC activity(%)
0
0.01
0.1
1
10
Antibody concentration(μg/ml)

Fig. 35B

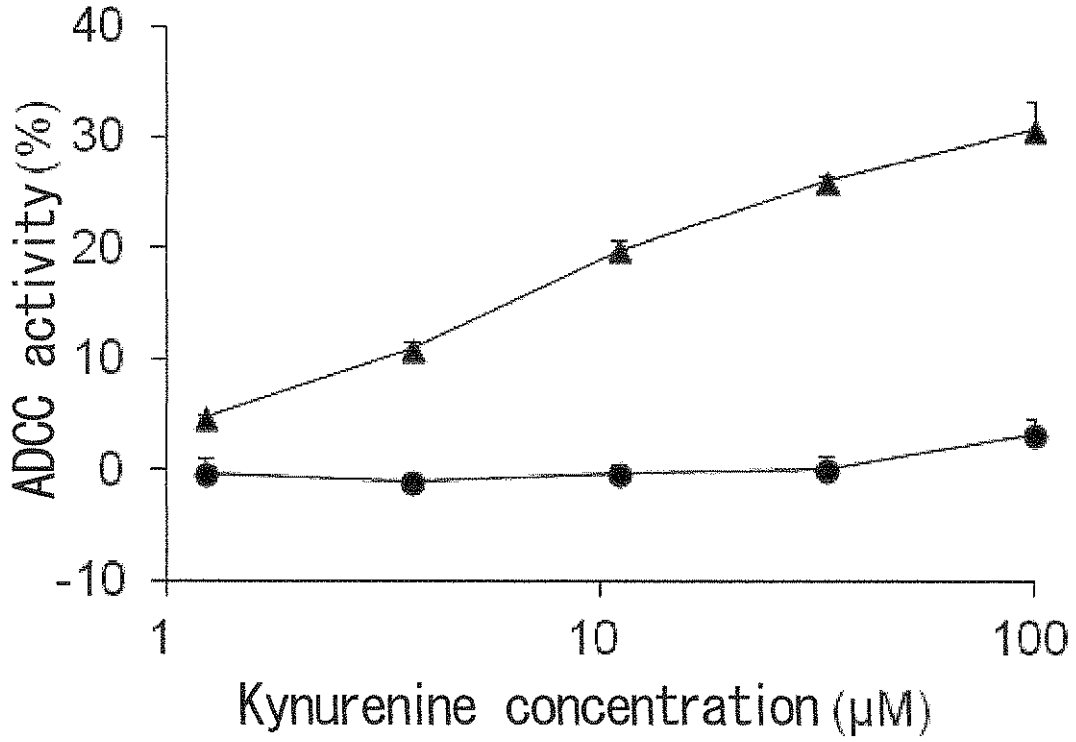

40
30
20
10
0
-10
ADCC activity(%)
1
10
100
Kynurenine concentration (μM)

Fig. 36

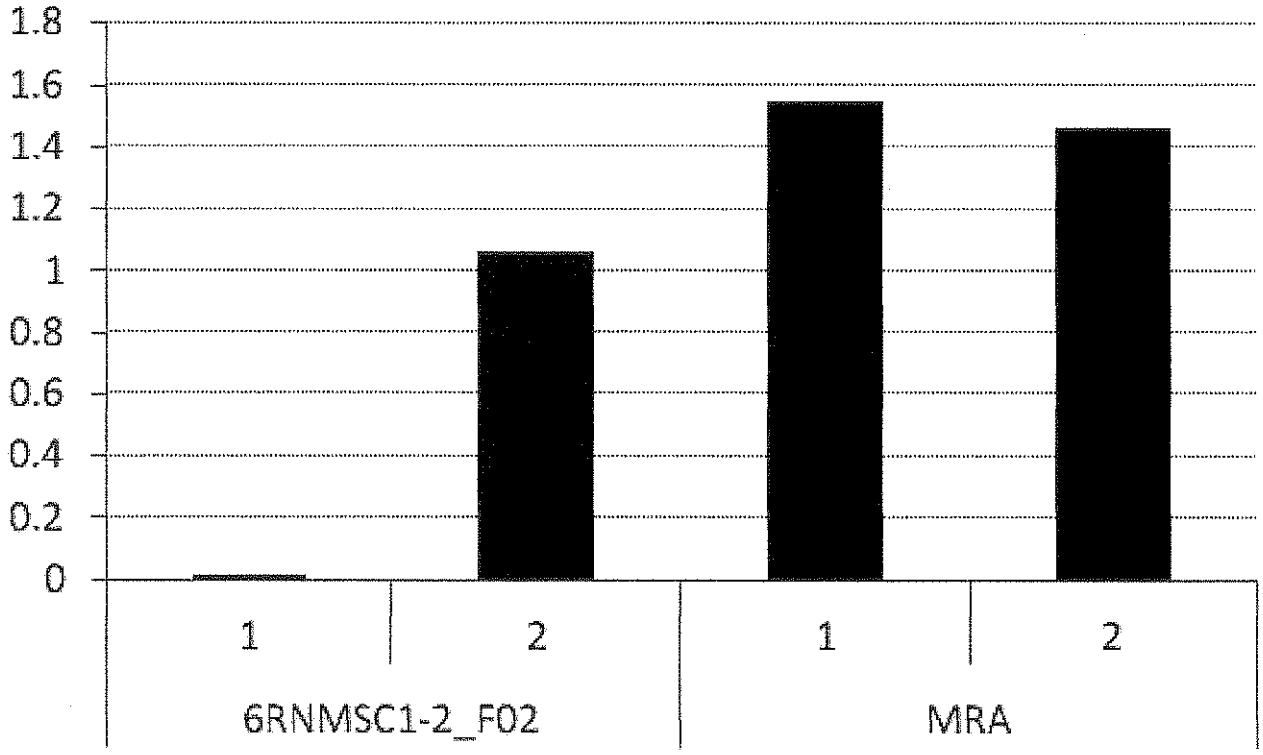


Fig. 37

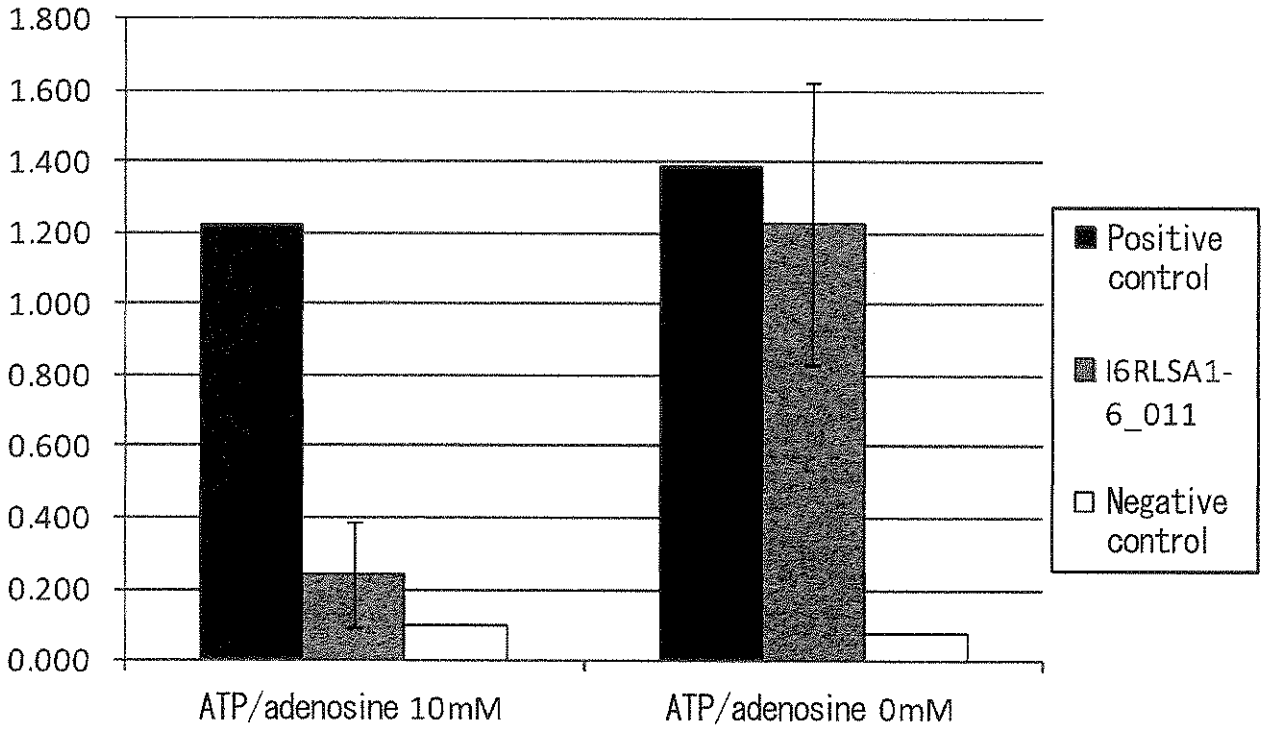

1.800
1.600
1.400
1.200
1.000
0.800
0.600
0.400
0.200
0.000
ATP/adenosine 10mM
ATP/adenosine 0mM
Positive control
I6RLSA1-6_011
Negative control

Fig. 38

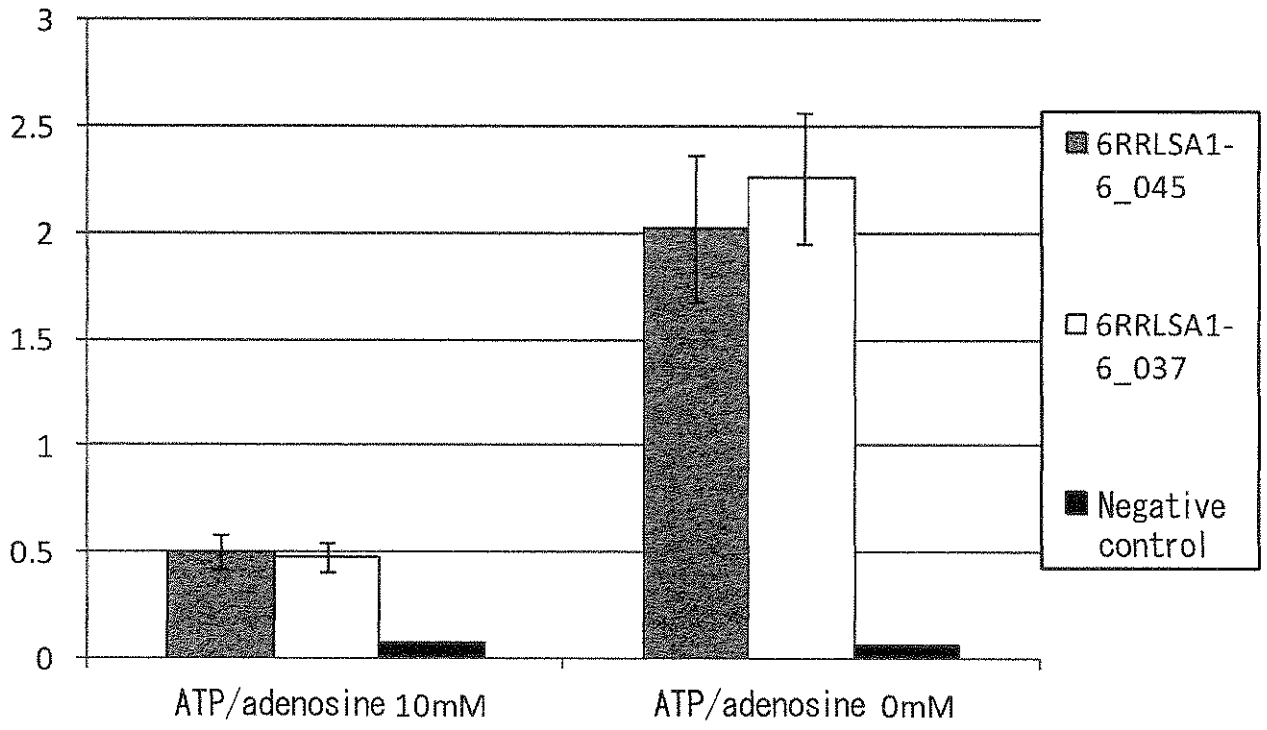

3
2.5
2
1.5
1
0.5
0
ATP/adenosine 10mM
ATP/adenosine 0mM
6RRLSA1-6_045
6RRLSA1-6_037
Negative control

Fig. 39

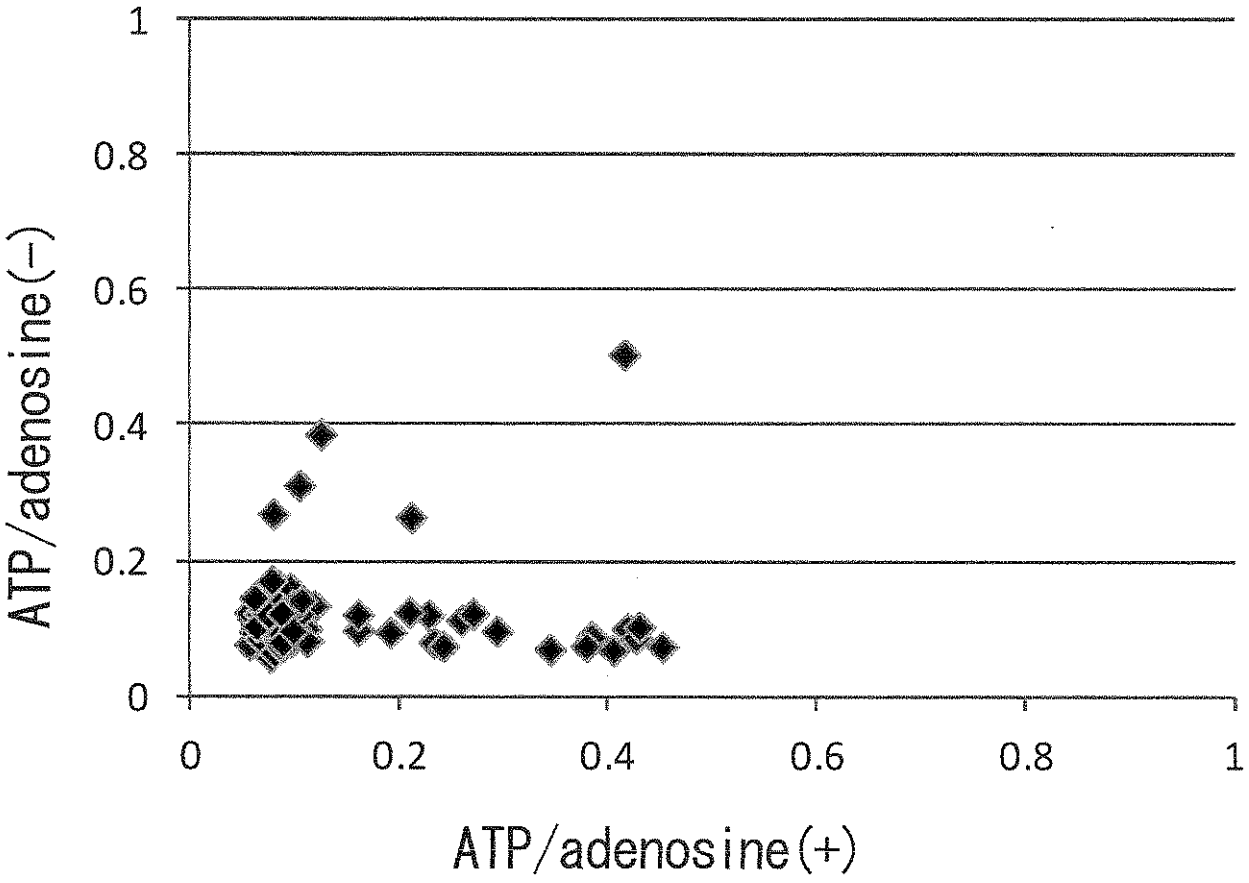


Fig. 40

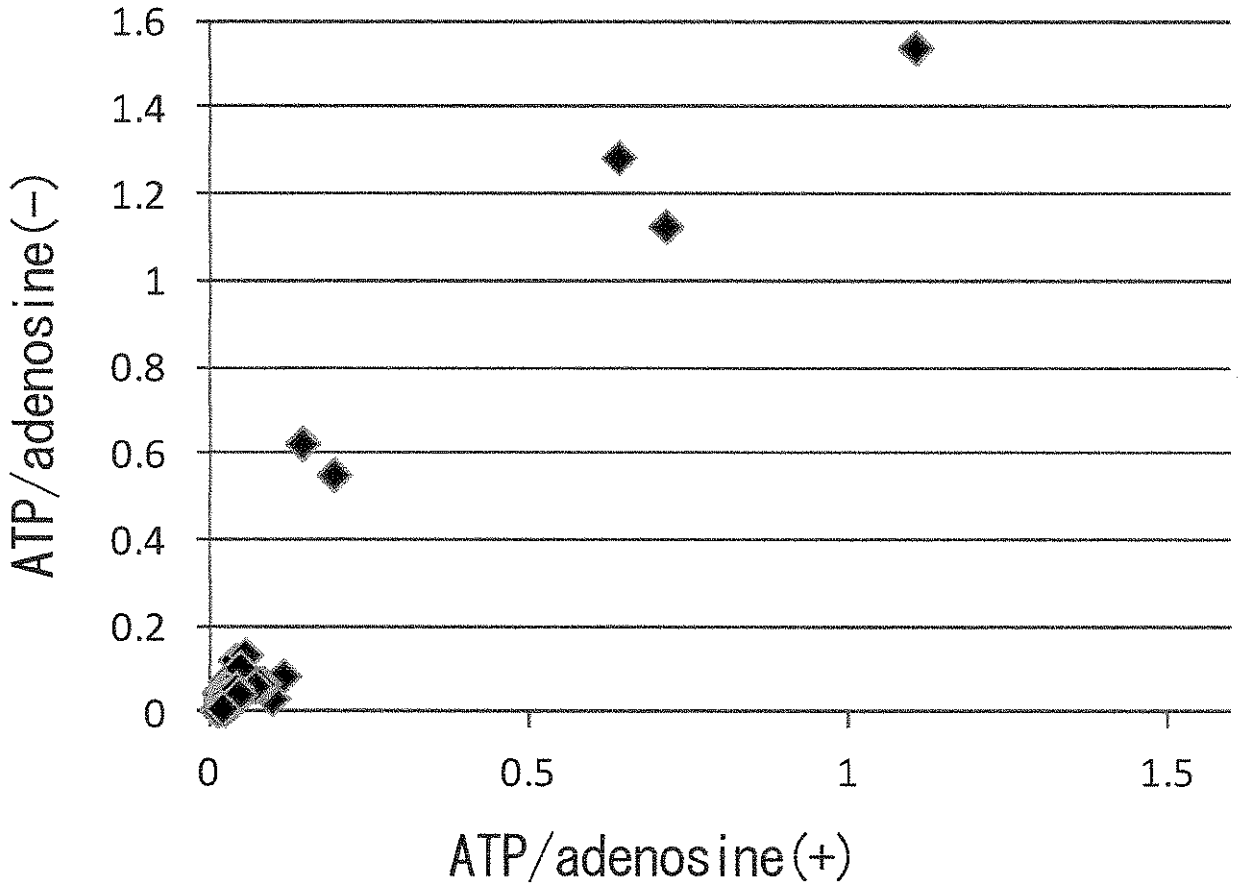


Fig. 41

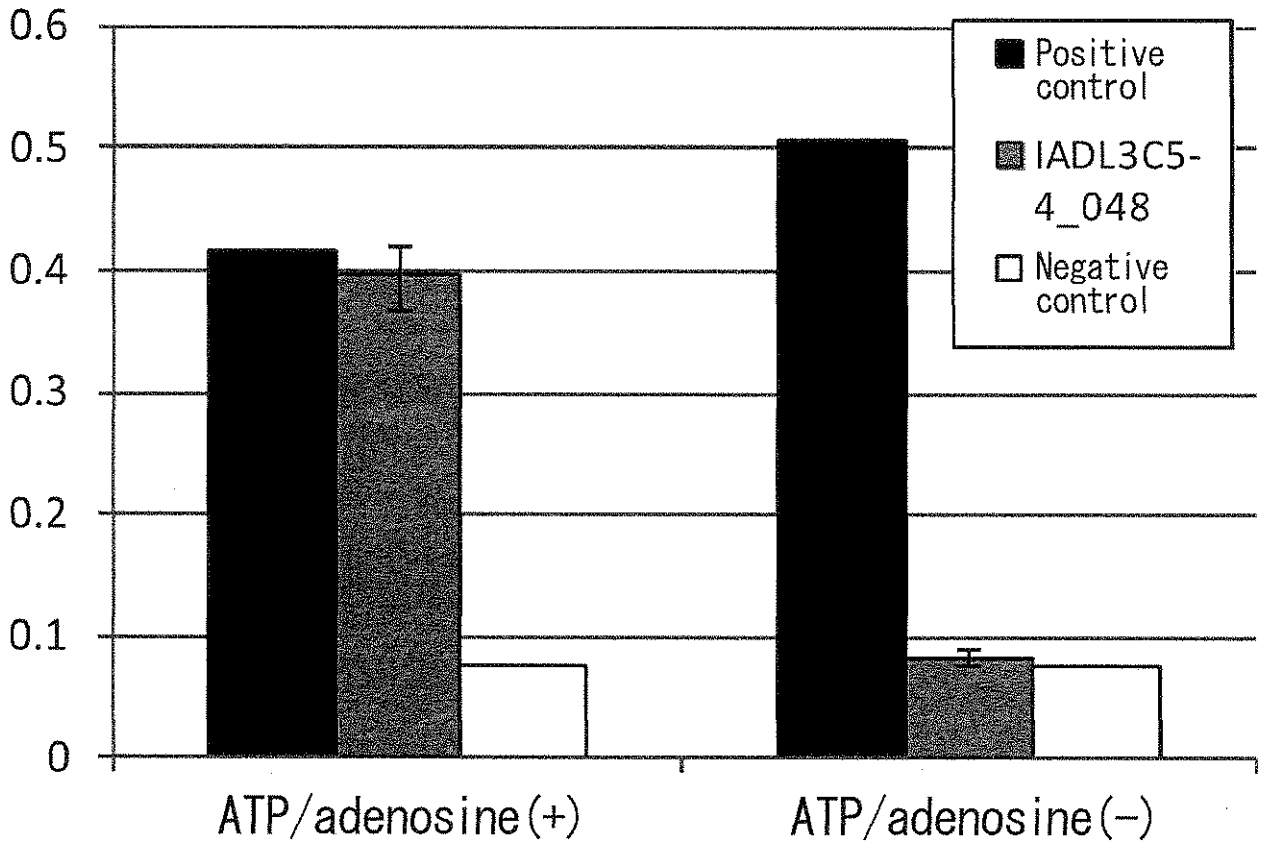

0.6
0.5
0.4
0.3
0.2
0.1
0
Positive control
IADL3C5-4_048
Negative control
ATP/adenosine(+)
ATP/adenosine(−)

Fig. 42

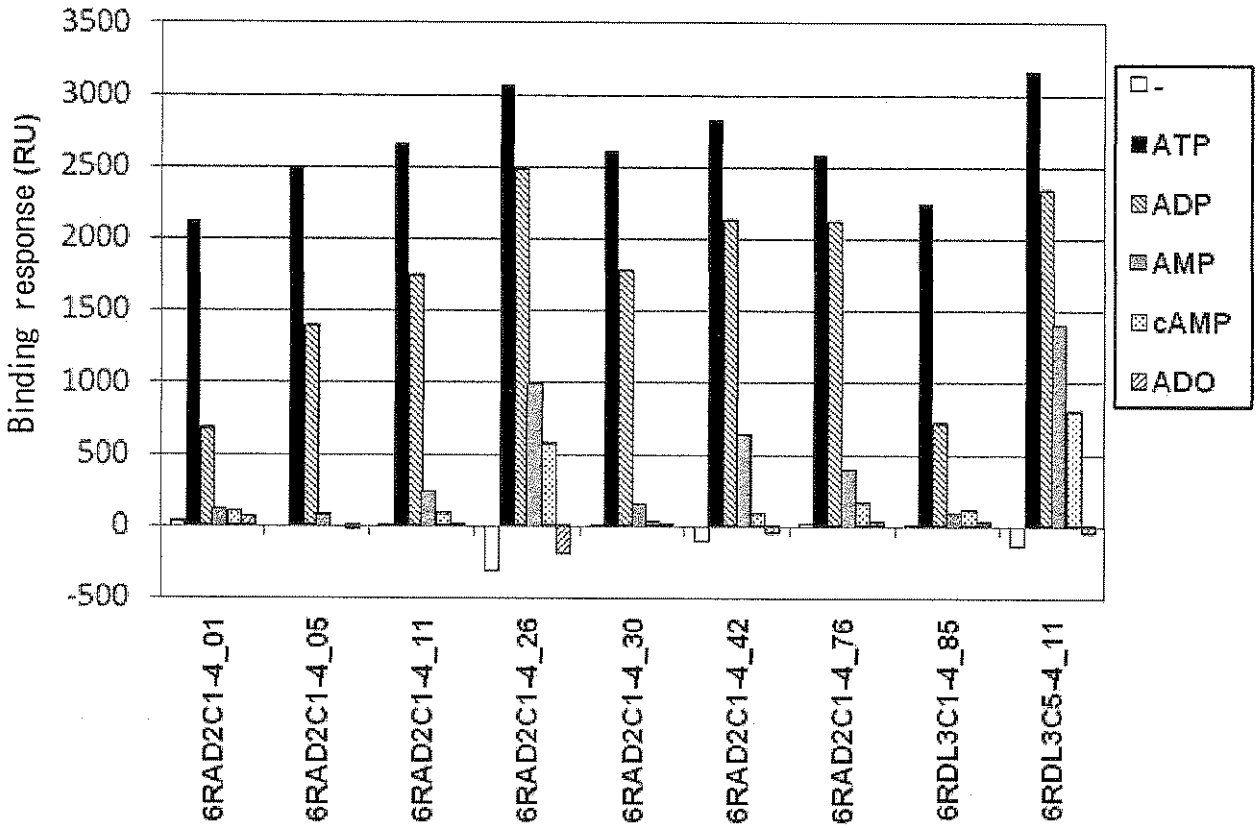

Binding response (RU)
3500
3000
2500
2000
1500
1000
500
0
-500
-
ATP
ADP
AMP
cAMP
ADO
6RAD2C1-4_01
6RAD2C1-4_05
6RAD2C1-4_11
6RAD2C1-4_26
6RAD2C1-4_30
6RAD2C1-4_42
6RAD2C1-4_76
6RDL3C1-4_85
6RDL3C5-4_11

Fig. 43

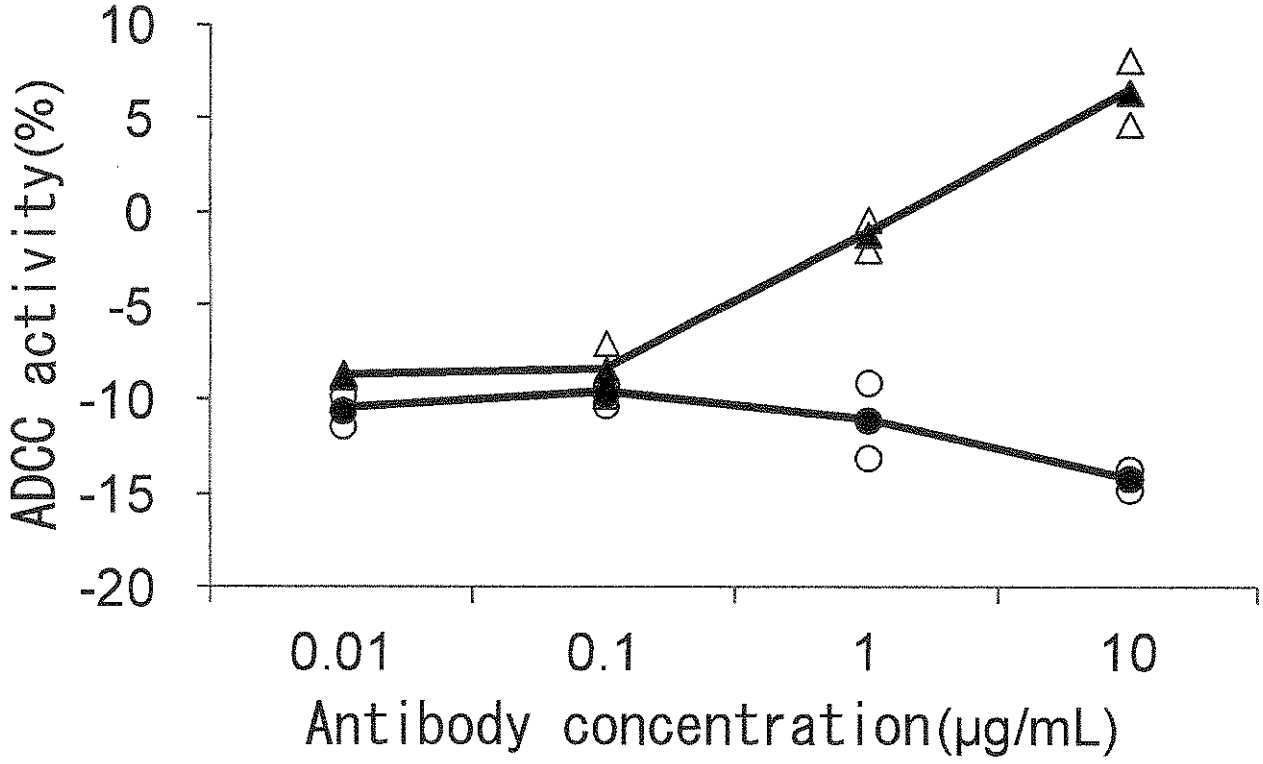

10
5
0
-5
-10
-15
-20
ADCC activity(%)
0.01
0.1
1
10
Antibody concentration(μg/mL)

Fig. 44A

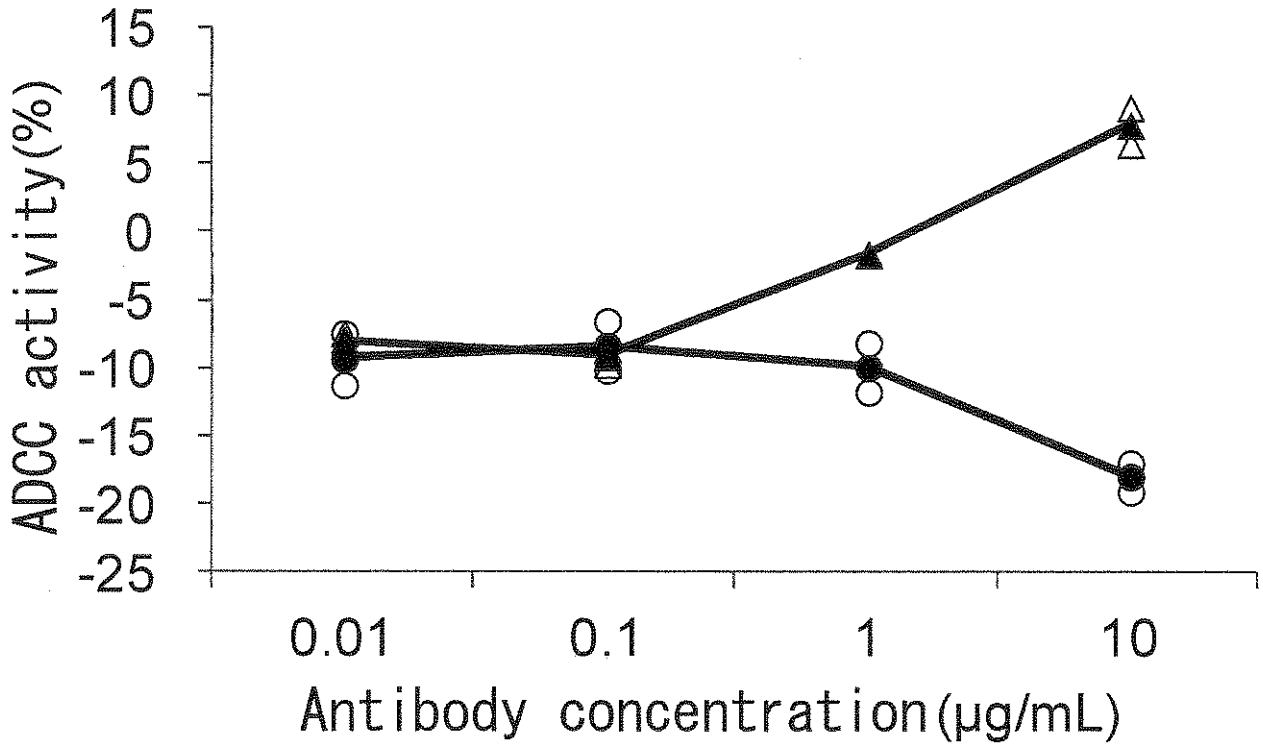

15
10
5
0
-5
-10
-15
-20
-25
ADCC activity(%)
0.01
0.1
1
10
Antibody concentration(μg/mL)

Fig. 44B

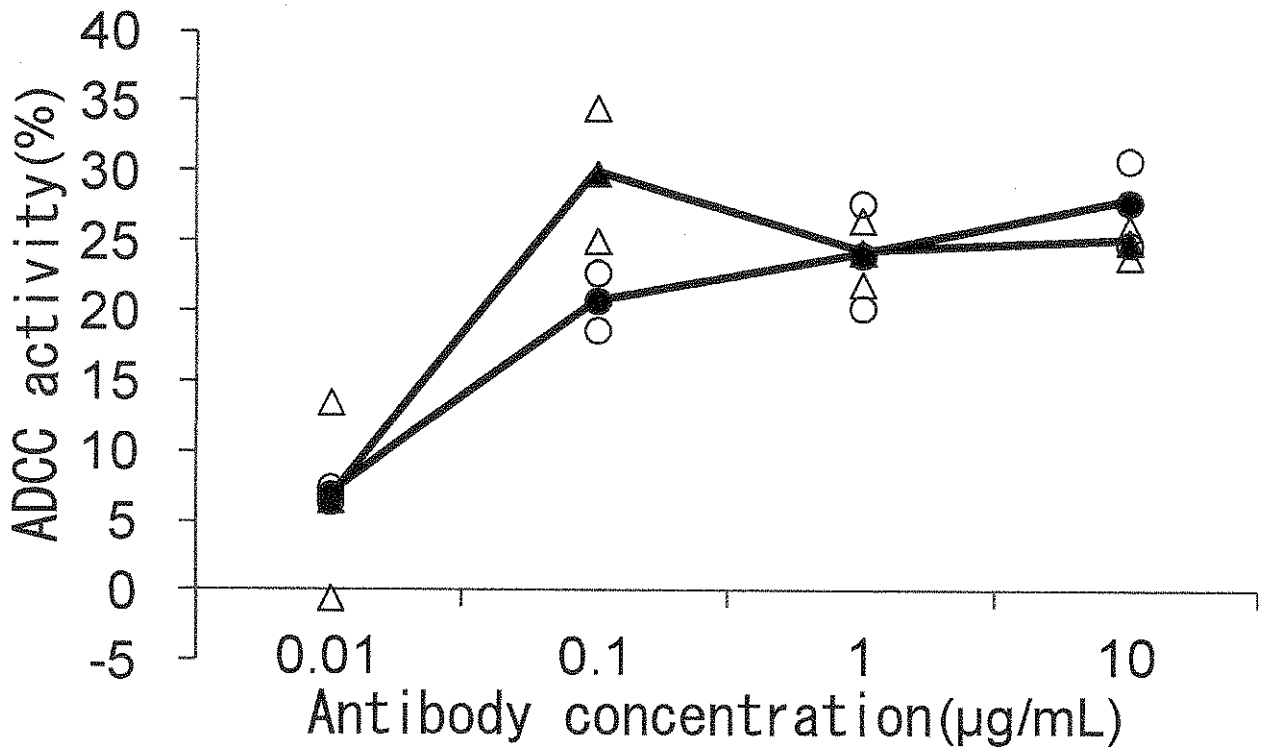

ADCC activity(%)
40
35
30
25
20
15
10
5
0
-5
0.01
0.1
1
10
Antibody concentration(μg/mL)

Fig. 44C

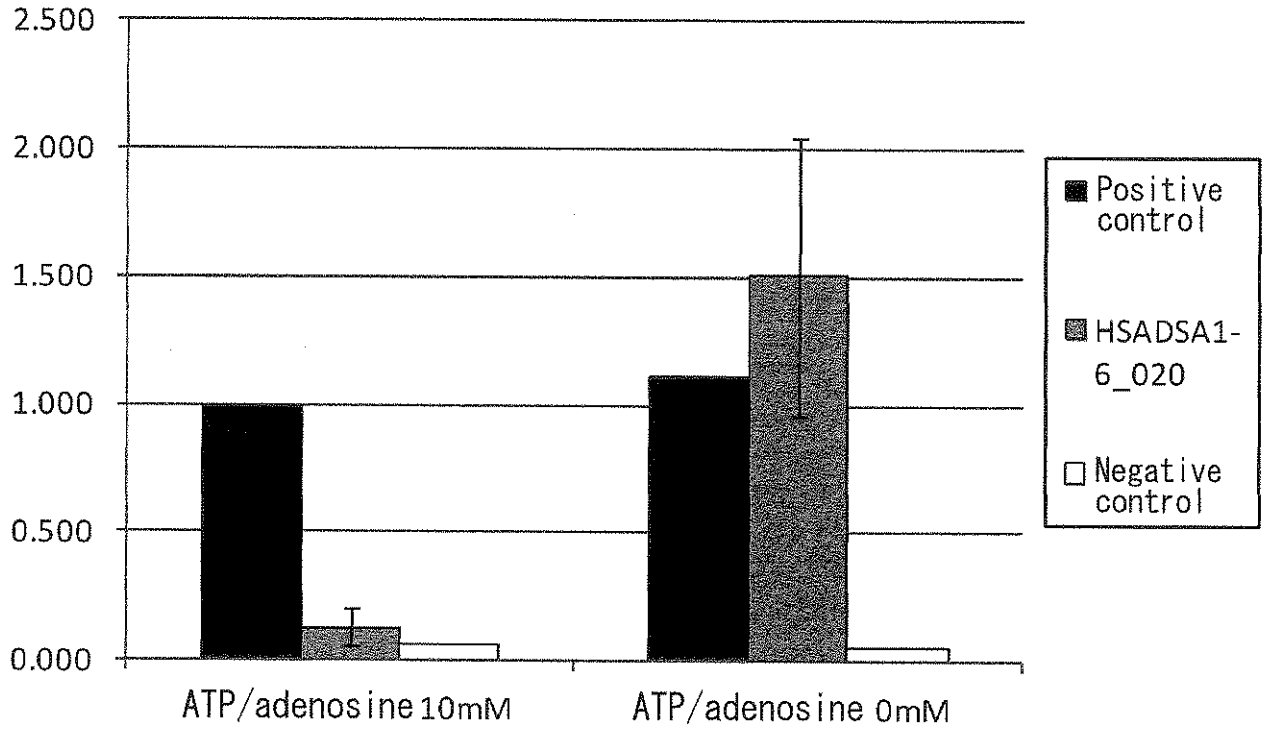

2.500
2.000
1.500
1.000
0.500
0.000
ATP/adenosine 10mM
ATP/adenosine 0mM
Positive control
HSADSA1-6_020
Negative control

Fig. 45