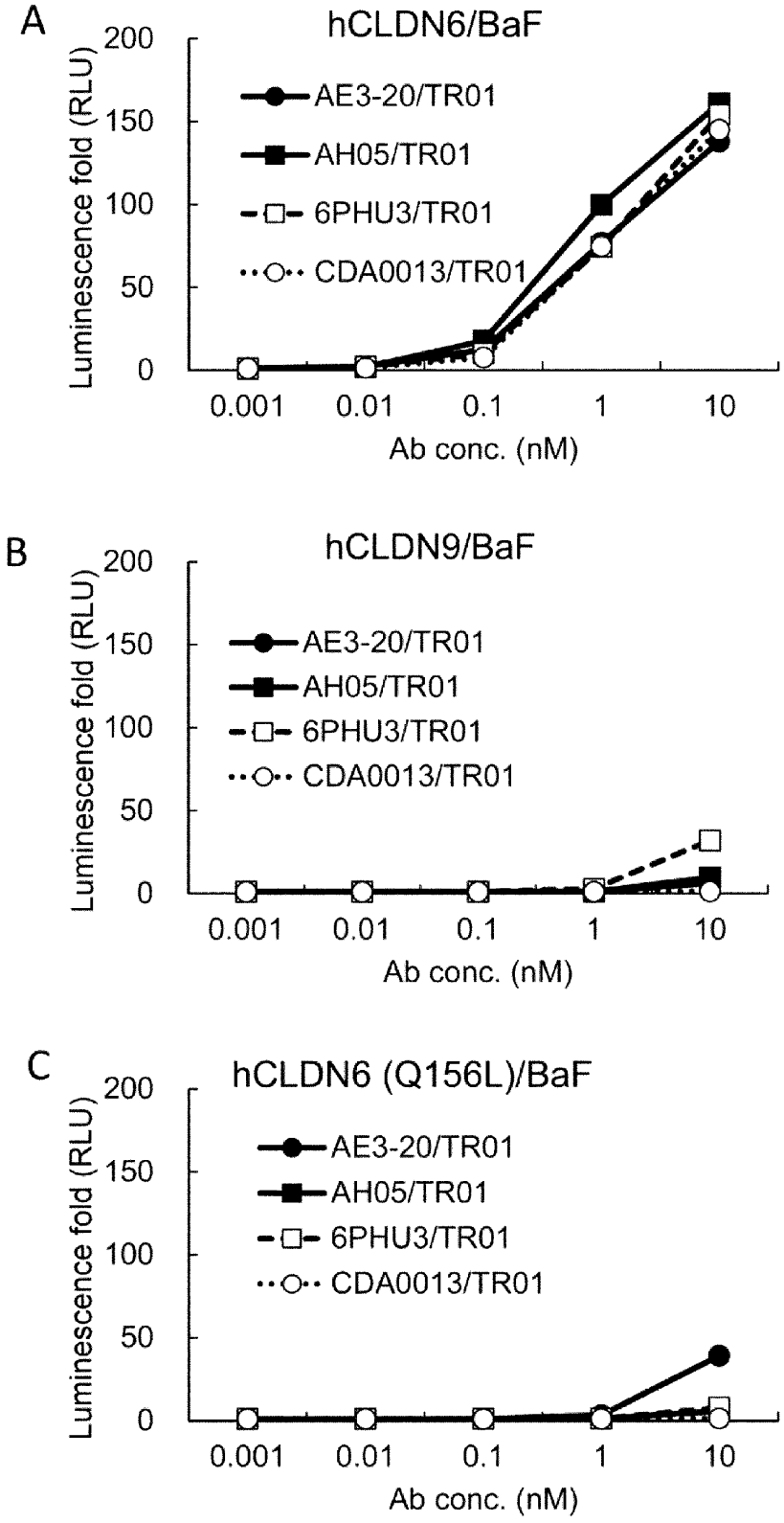
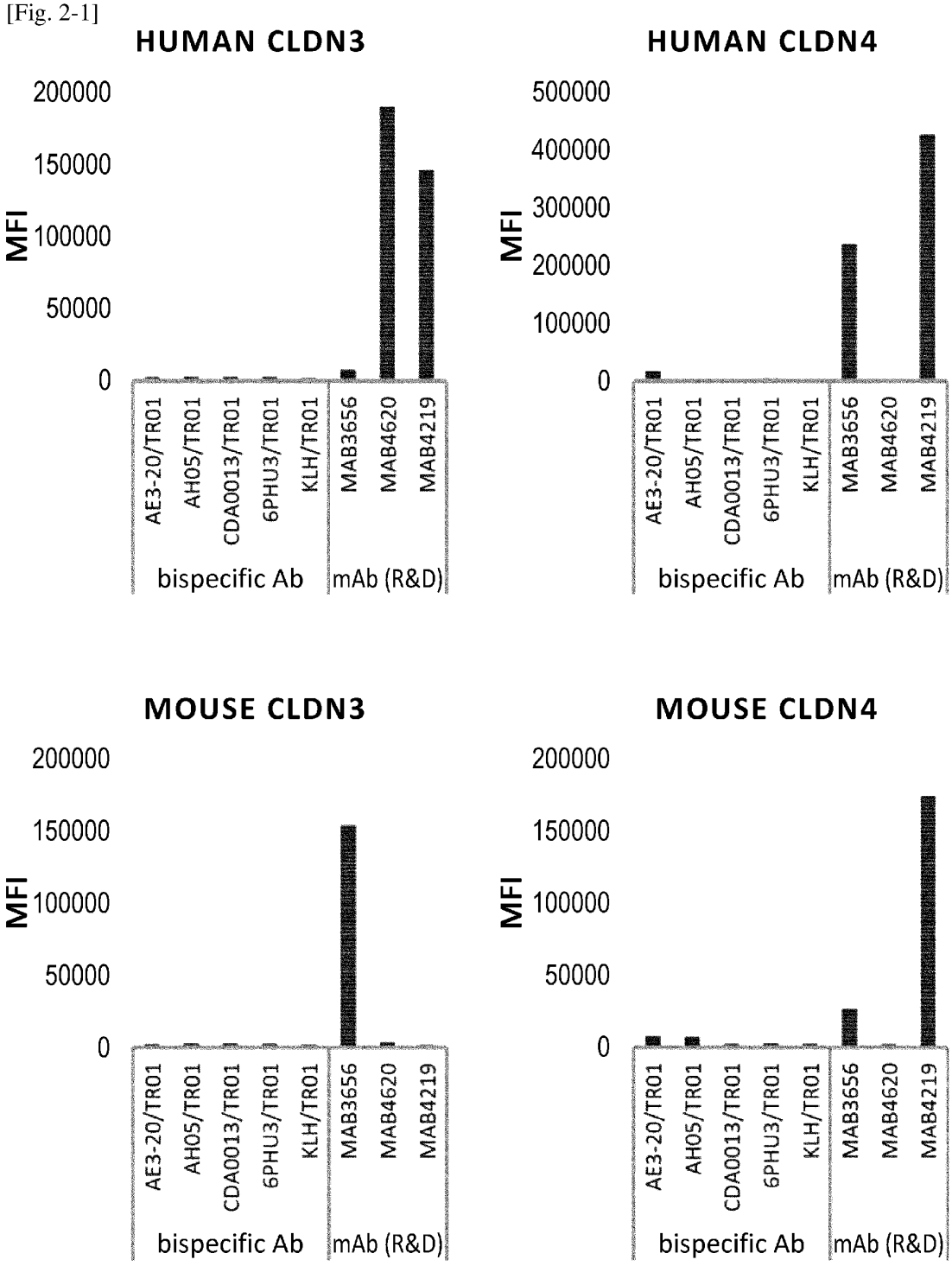
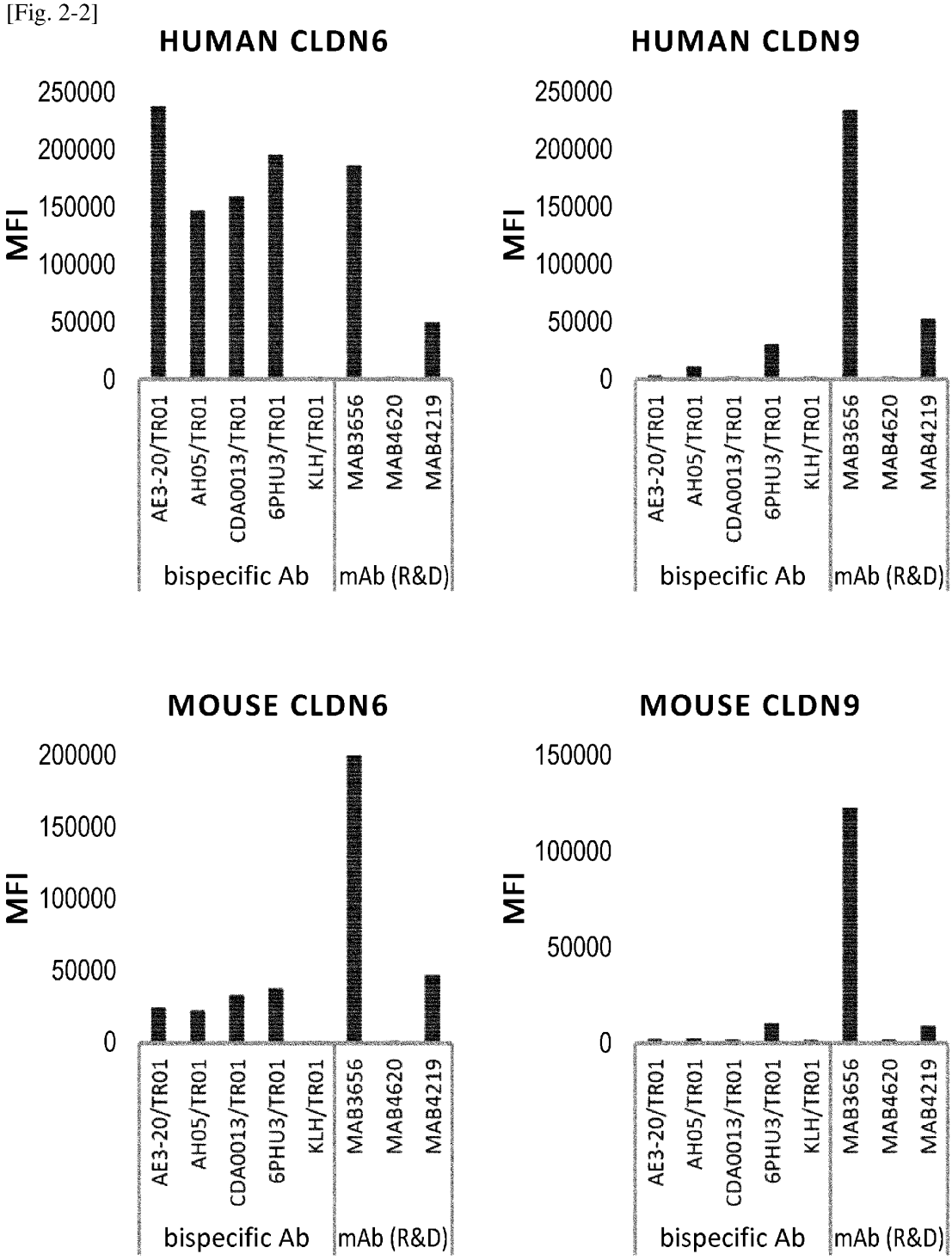
[Fig. 1]


A
hCLDN6/BaF
Luminescence fold (RLU)
200
150
100
50
0
AE3-20/TR01
AH05/TR01
6PHU3/TR01
CDA0013/TR01
0.001
0.01
0.1
1
10
Ab conc. (nM)
B
hCLDN9/BaF
Luminescence fold (RLU)
200
150
100
50
0
AE3-20/TR01
AH05/TR01
6PHU3/TR01
CDA0013/TR01
0.001
0.01
0.1
1
10
Ab conc. (nM)
C
hCLDN6 (Q156L)/BaF
Luminescence fold (RLU)
200
150
100
50
0
AE3-20/TR01
AH05/TR01
6PHU3/TR01
CDA0013/TR01
0.001
0.01
0.1
1
10
Ab conc. (nM)

[Fig. 2-1]

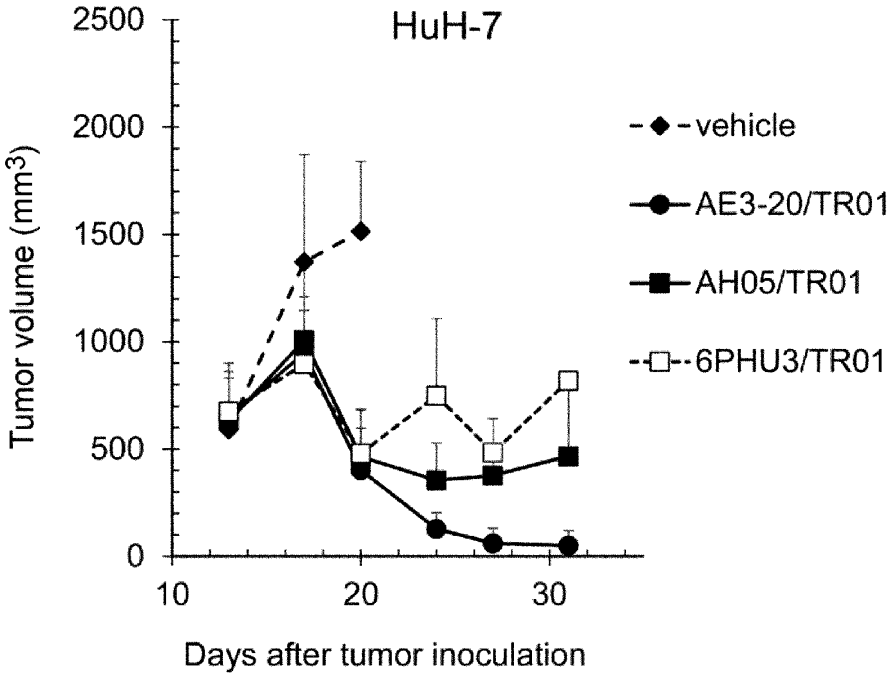

HUMAN CLDN3
MFI
200000
150000
100000
50000
0
AE3-20/TR01
AH05/TR01
CDA0013/TR01
6PHU3/TR01
KLH/TR01
MAB3656
MAB4620
MAB4219
bispecific Ab
mAb (R&D)
HUMAN CLDN4
MFI
500000
400000
300000
200000
100000
0
AE3-20/TR01
AH05/TR01
CDA0013/TR01
6PHU3/TR01
KLH/TR01
MAB3656
MAB4620
MAB4219
bispecific Ab
mAb (R&D)
MOUSE CLDN3
MFI
200000
150000
100000
50000
0
AE3-20/TR01
AH05/TR01
CDA0013/TR01
6PHU3/TR01
KLH/TR01
MAB3656
MAB4620
MAB4219
bispecific Ab
mAb (R&D)
MOUSE CLDN4
MFI
200000
150000
100000
50000
0
AE3-20/TR01
AH05/TR01
CDA0013/TR01
6PHU3/TR01
KLH/TR01
MAB3656
MAB4620
MAB4219
bispecific Ab
mAb (R&D)

[Fig. 2-2]

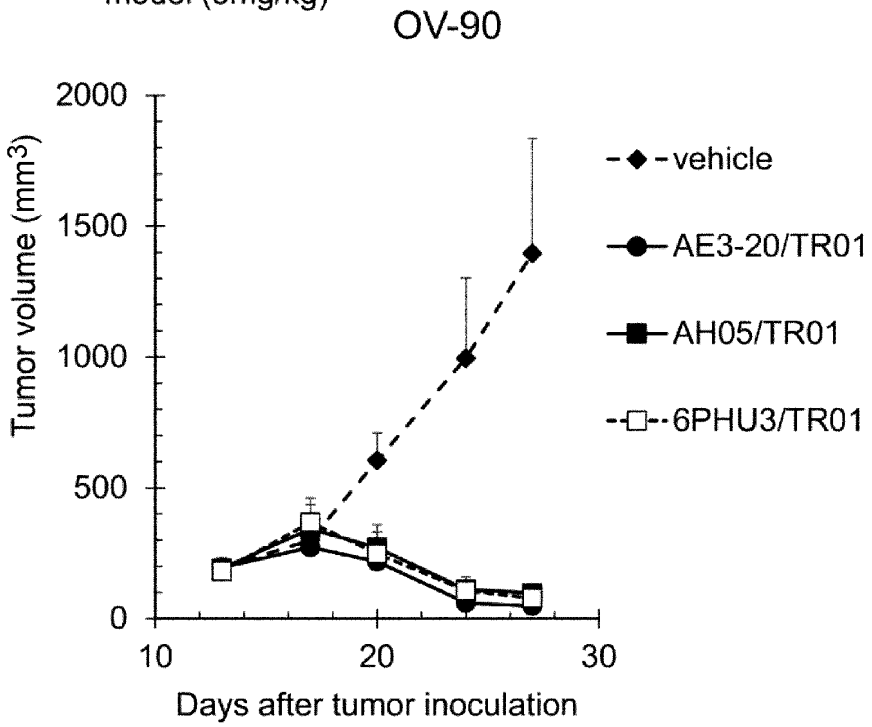

HUMAN CLDN6
MFI
250000
200000
150000
100000
50000
0
AE3-20/TR01
AH05/TR01
CDA0013/TR01
6PHU3/TR01
KLH/TR01
MAB3656
MAB4620
MAB4219
bispecific Ab
mAb (R&D)
HUMAN CLDN9
MFI
250000
200000
150000
100000
50000
0
AE3-20/TR01
AH05/TR01
CDA0013/TR01
6PHU3/TR01
KLH/TR01
MAB3656
MAB4620
MAB4219
bispecific Ab
mAb (R&D)
MOUSE CLDN6
MFI
200000
150000
100000
50000
0
AE3-20/TR01
AH05/TR01
CDA0013/TR01
6PHU3/TR01
KLH/TR01
MAB3656
MAB4620
MAB4219
bispecific Ab
mAb (R&D)
MOUSE CLDN9
MFI
150000
100000
50000
0
AE3-20/TR01
AH05/TR01
CDA0013/TR01
6PHU3/TR01
KLH/TR01
MAB3656
MAB4620
MAB4219
bispecific Ab
mAb (R&D)

[Fig. 3]

■ a. Tumor volume change in HuH-7 T cell injection model (5mg/kg)

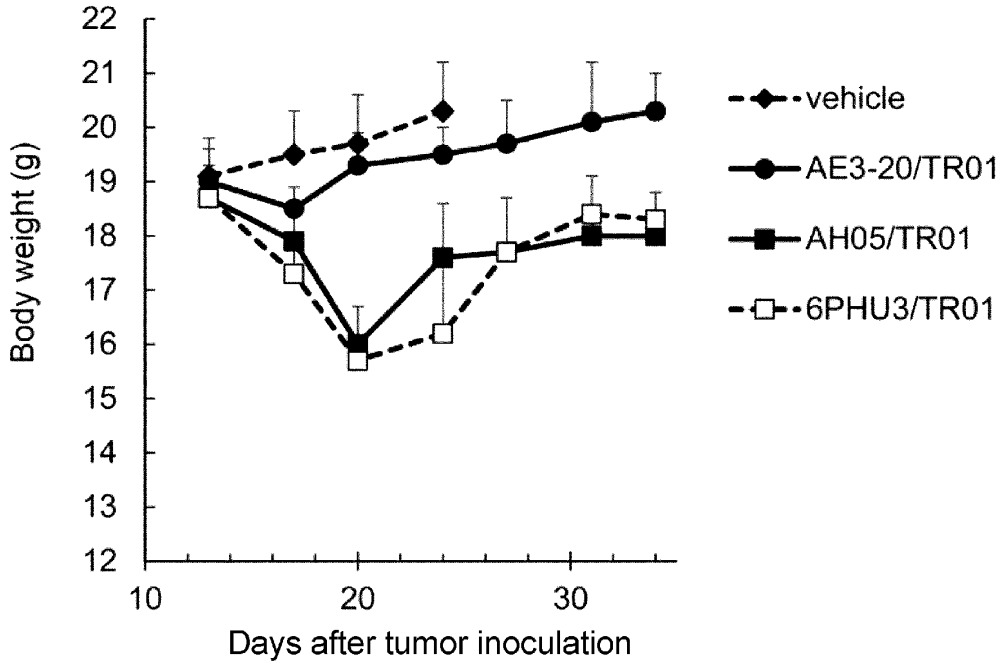


■ b. Tumor volume change in OV-90 T cell injection model (5mg/kg)

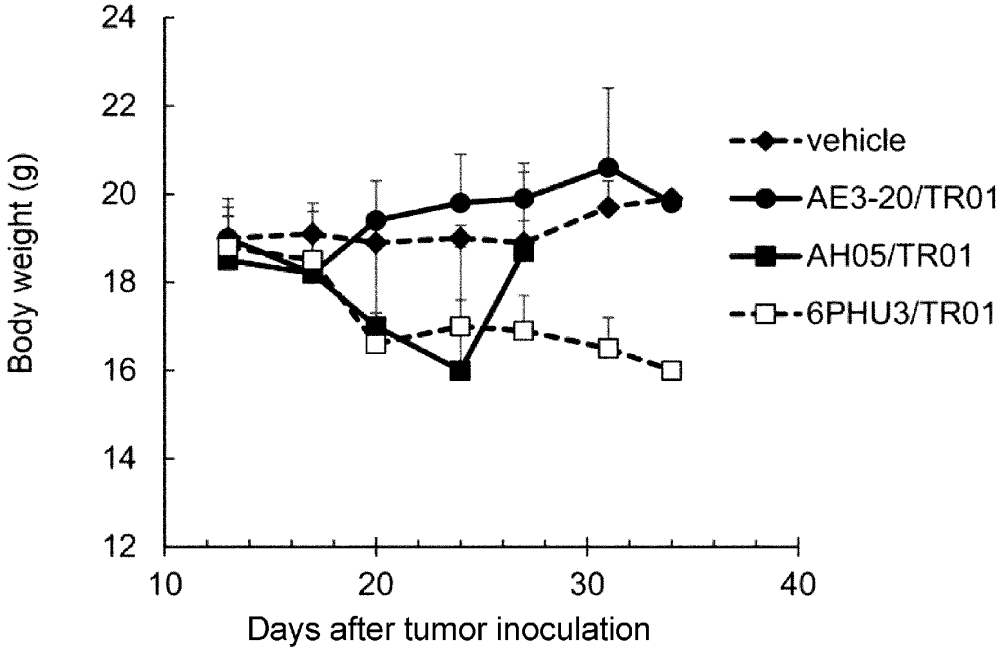


[Fig. 4]

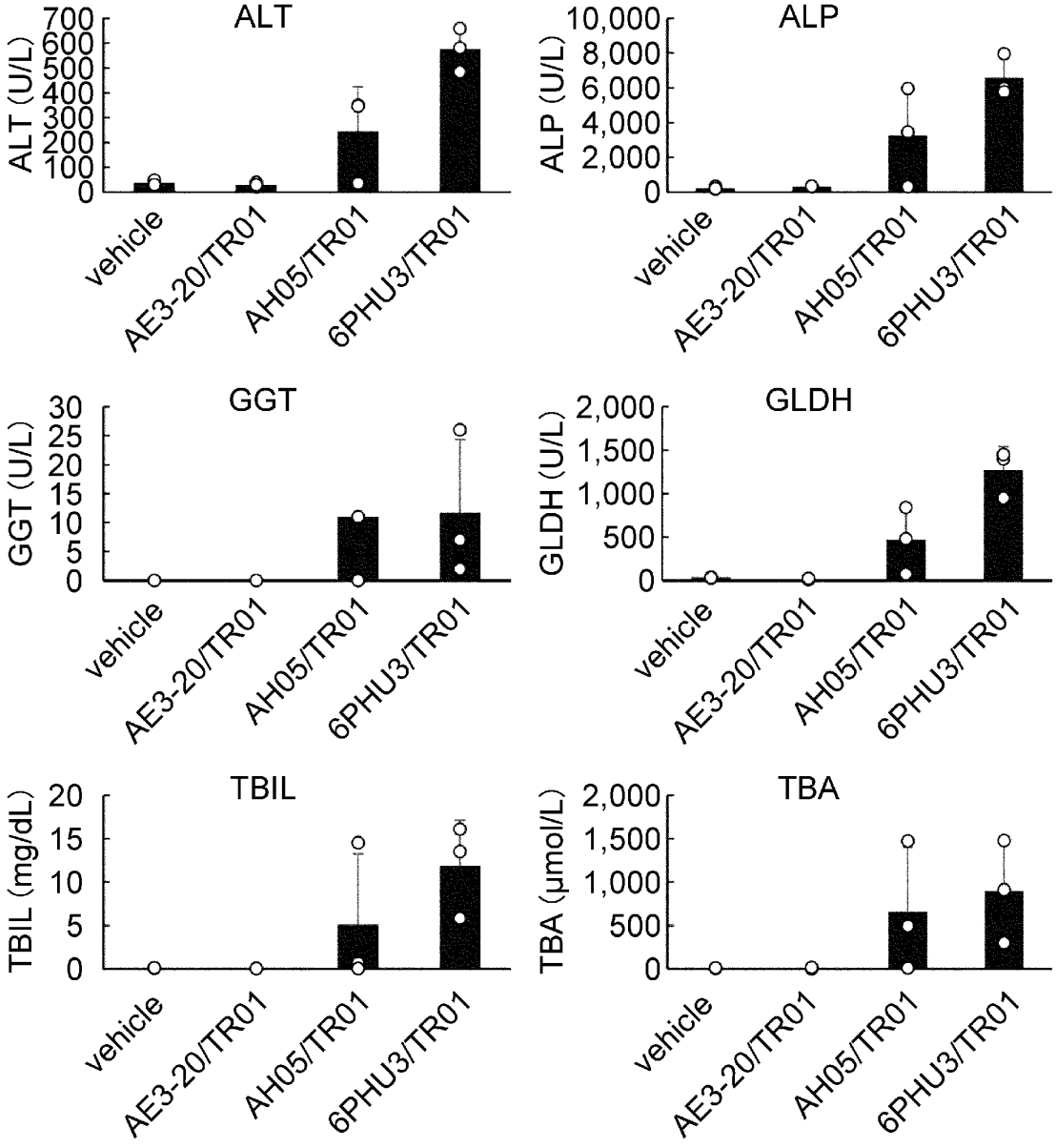
a. Body weight change in HuH7 T cell injection model (5mg/kg)



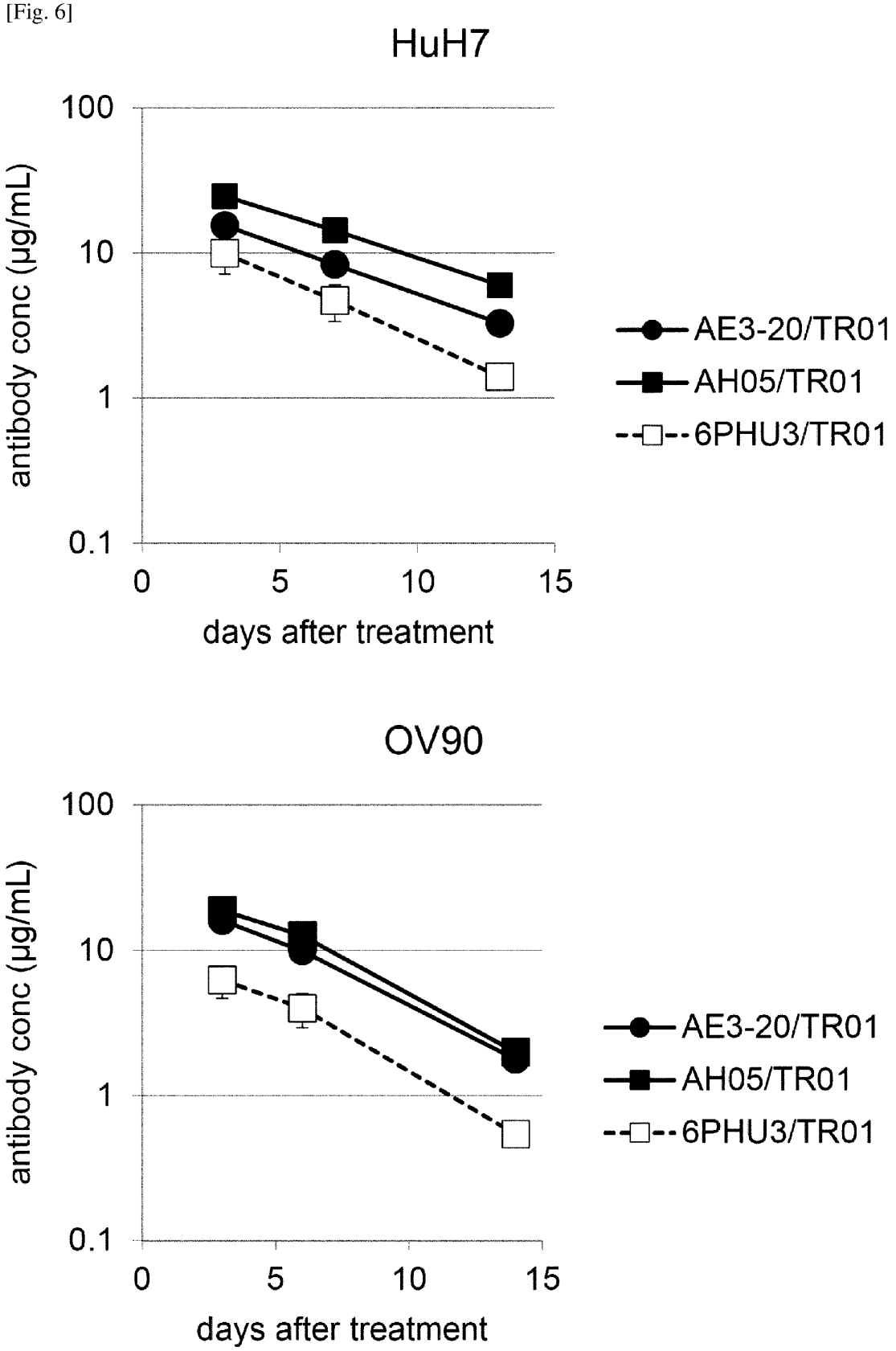
b. Body weight change in OV90 T cell injection model (5mg/kg)



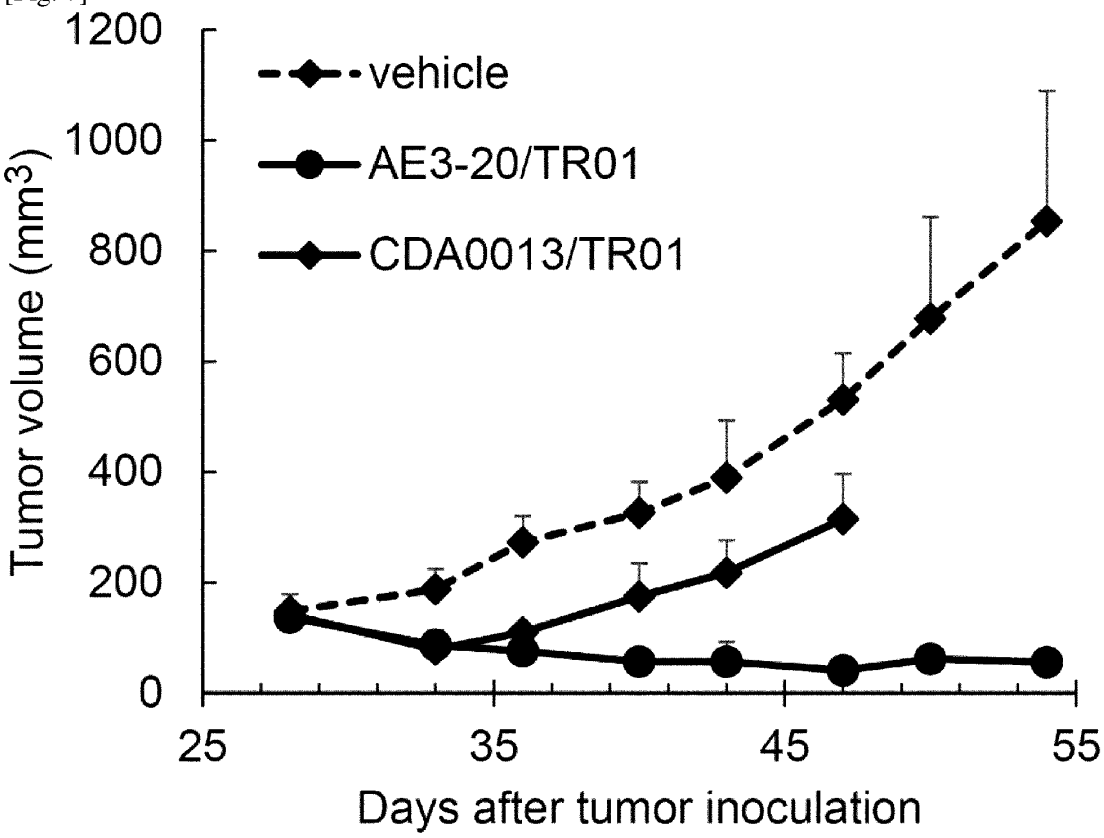
[Fig. 5]

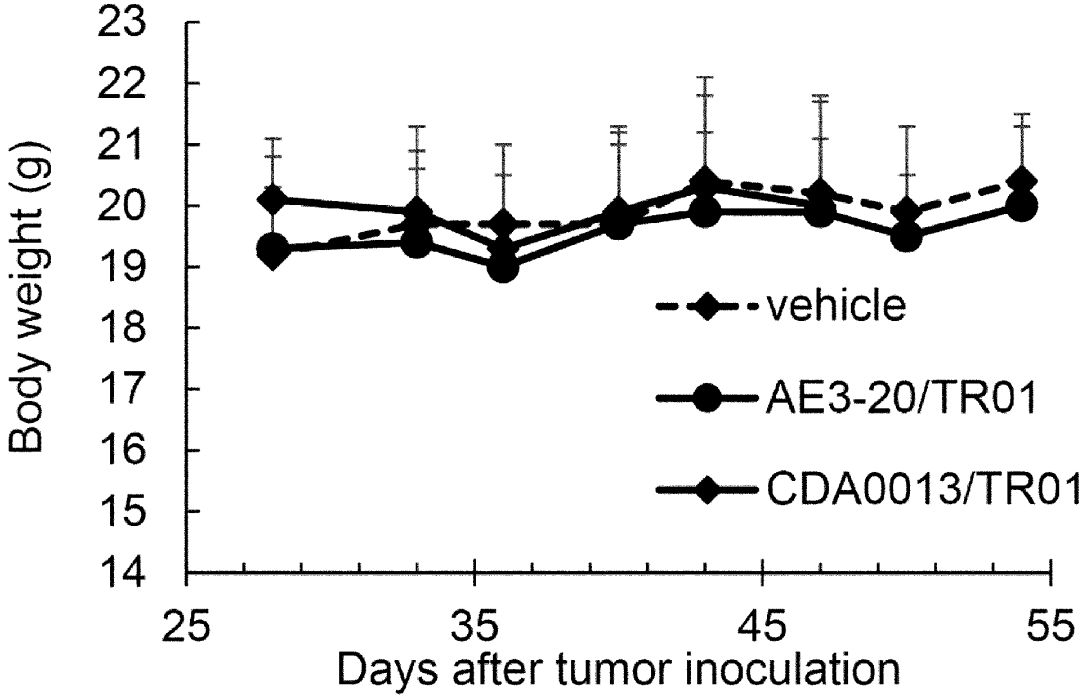

ALT
ALT (U/L)
700
600
500
400
300
200
100
0
ALP
ALP (U/L)
10,000
8,000
6,000
4,000
2,000
0
GGT
GGT (U/L)
30
25
20
15
10
5
0
GLDH
GLDH (U/L)
2,000
1,500
1,000
500
0
TBIL
TBIL (mg/dL)
20
15
10
5
0
TBA
TBA (μmol/L)
2,000
1,500
1,000
500
0
vehicle
AE3-20/TR01
AH05/TR01
6PHU3/TR01

[Fig. 6]

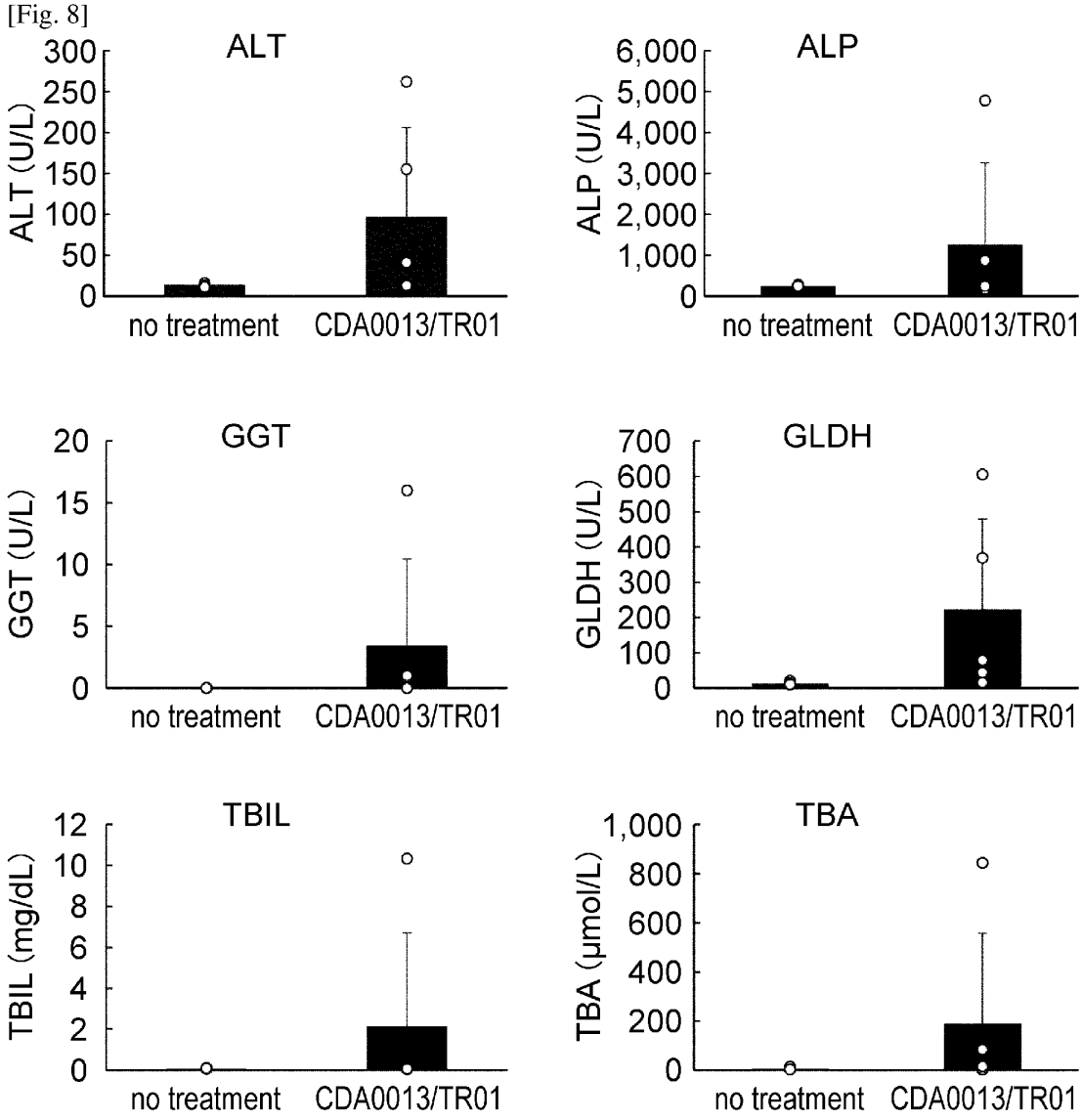

HuH7
100
10
1
0.1
antibody conc (μg/mL)
0
5
10
15
days after treatment
AE3-20/TR01
AH05/TR01
6PHU3/TR01
OV90
100
10
1
0.1
antibody conc (μg/mL)
0
5
10
15
days after treatment
AE3-20/TR01
AH05/TR01
6PHU3/TR01

[Fig. 7]

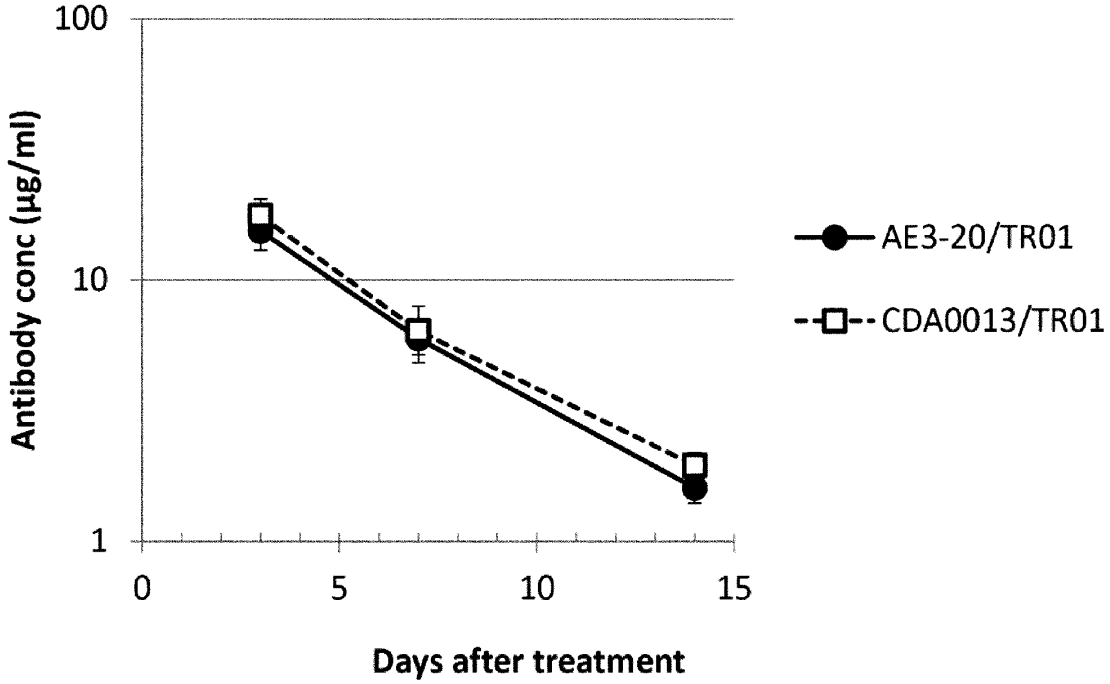

1200
1000
800
600
400
200
0
Tumor volume (mm3)
vehicle
AE3-20/TR01
CDA0013/TR01
25
35
45
55
Days after tumor inoculation


23
22
21
20
19
18
17
16
15
14
Body weight (g)
vehicle
AE3-20/TR01
CDA0013/TR01
25
35
45
55
Days after tumor inoculation

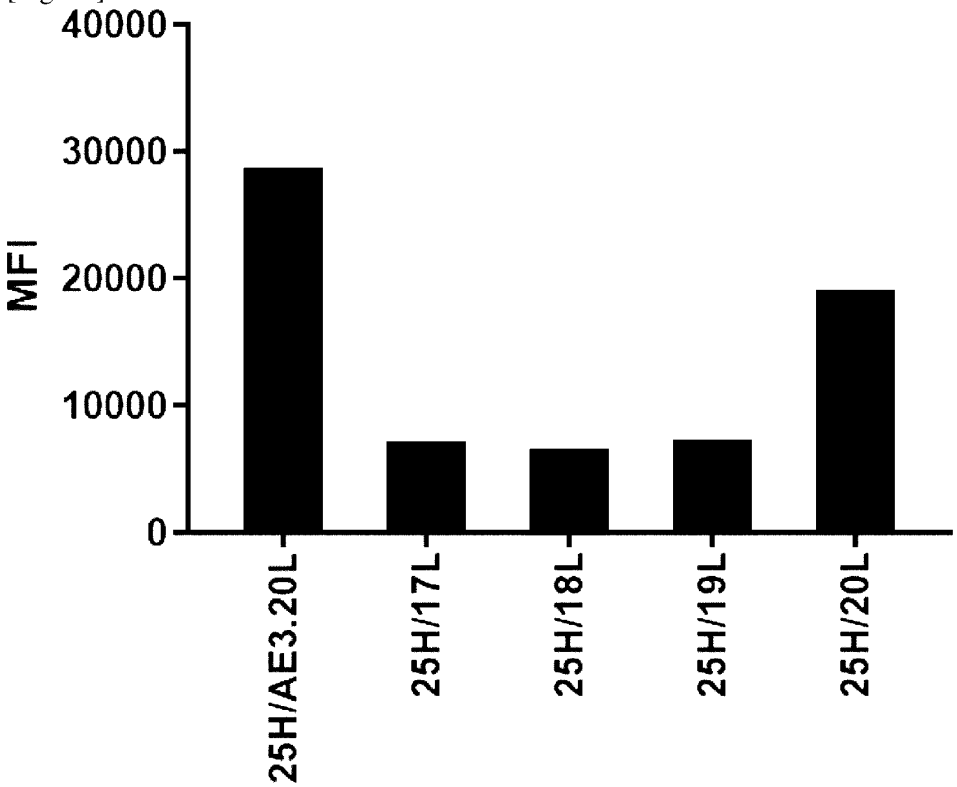
[Fig. 8]


ALT
ALT (U/L)
300
250
200
150
100
50
0
no treatment
CDA0013/TR01
ALP
ALP (U/L)
6,000
5,000
4,000
3,000
2,000
1,000
0
no treatment
CDA0013/TR01
GGT
GGT (U/L)
20
15
10
5
0
no treatment
CDA0013/TR01
GLDH
GLDH (U/L)
700
600
500
400
300
200
100
0
no treatment
CDA0013/TR01
TBIL
TBIL (mg/dL)
12
10
8
6
4
2
0
no treatment
CDA0013/TR01
TBA
TBA (μmol/L)
1,000
800
600
400
200
0
no treatment
CDA0013/TR01

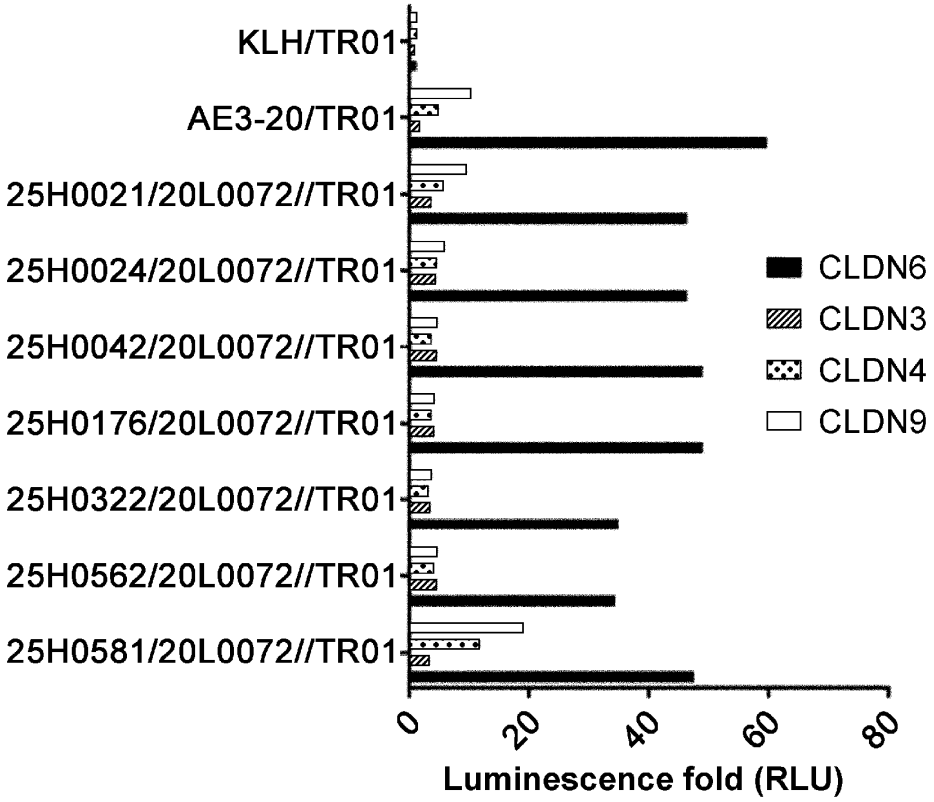
[Fig. 9]

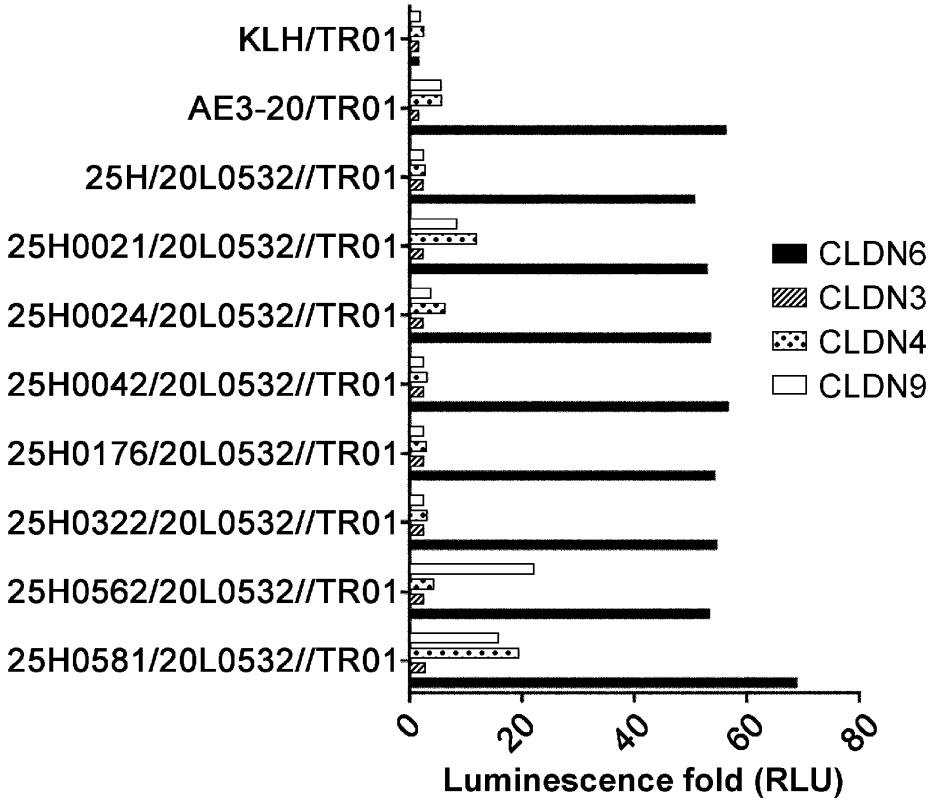

100
10
1
Antibody conc (μg/ml)
0
5
10
15
Days after treatment
AE3-20/TR01
CDA0013/TR01

[Fig. 10]

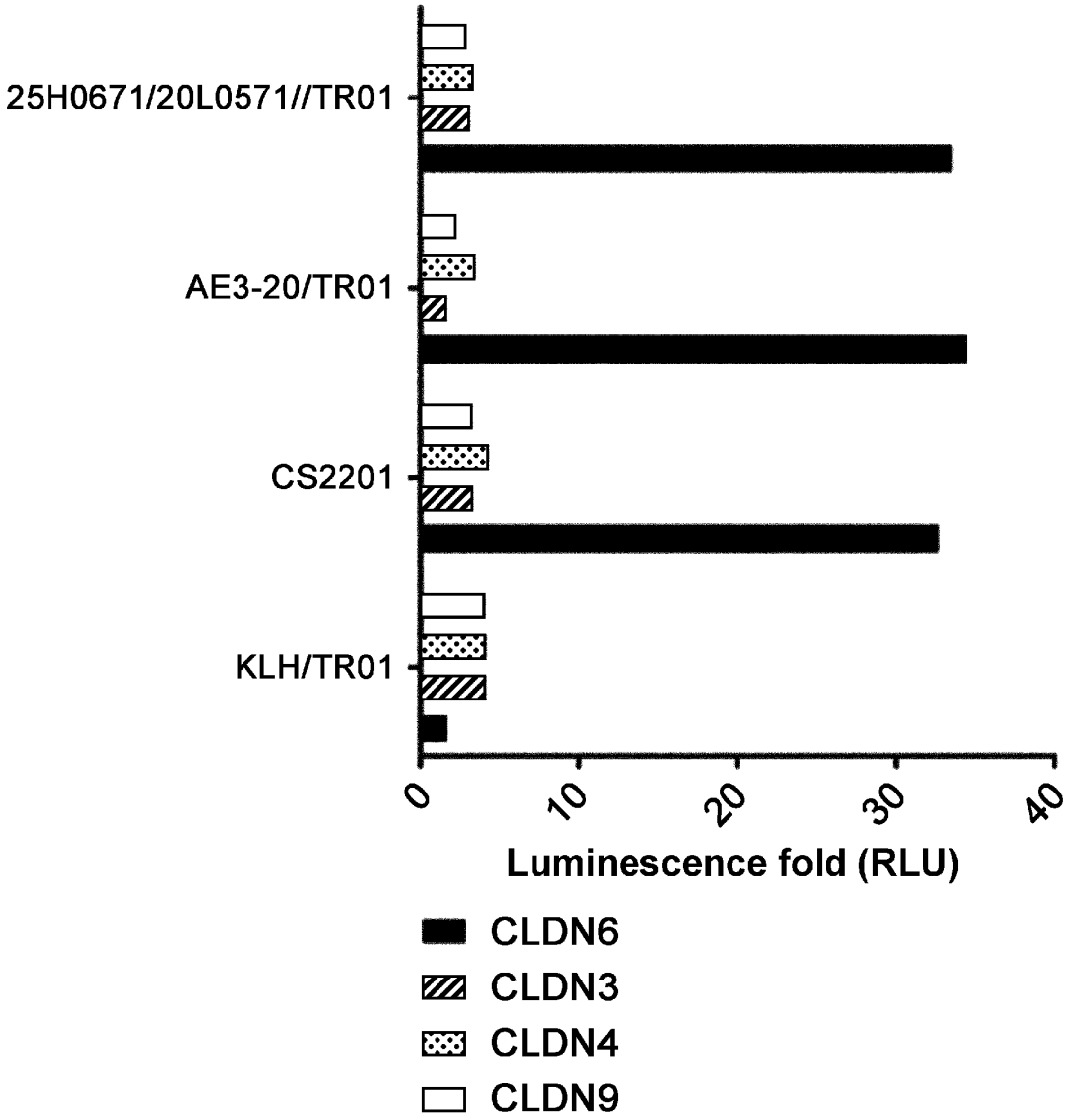

40000
30000
20000
10000
0
MFI
25H/AE3.20L
25H/17L
25H/18L
25H/19L
25H/20L

[Fig. 11]

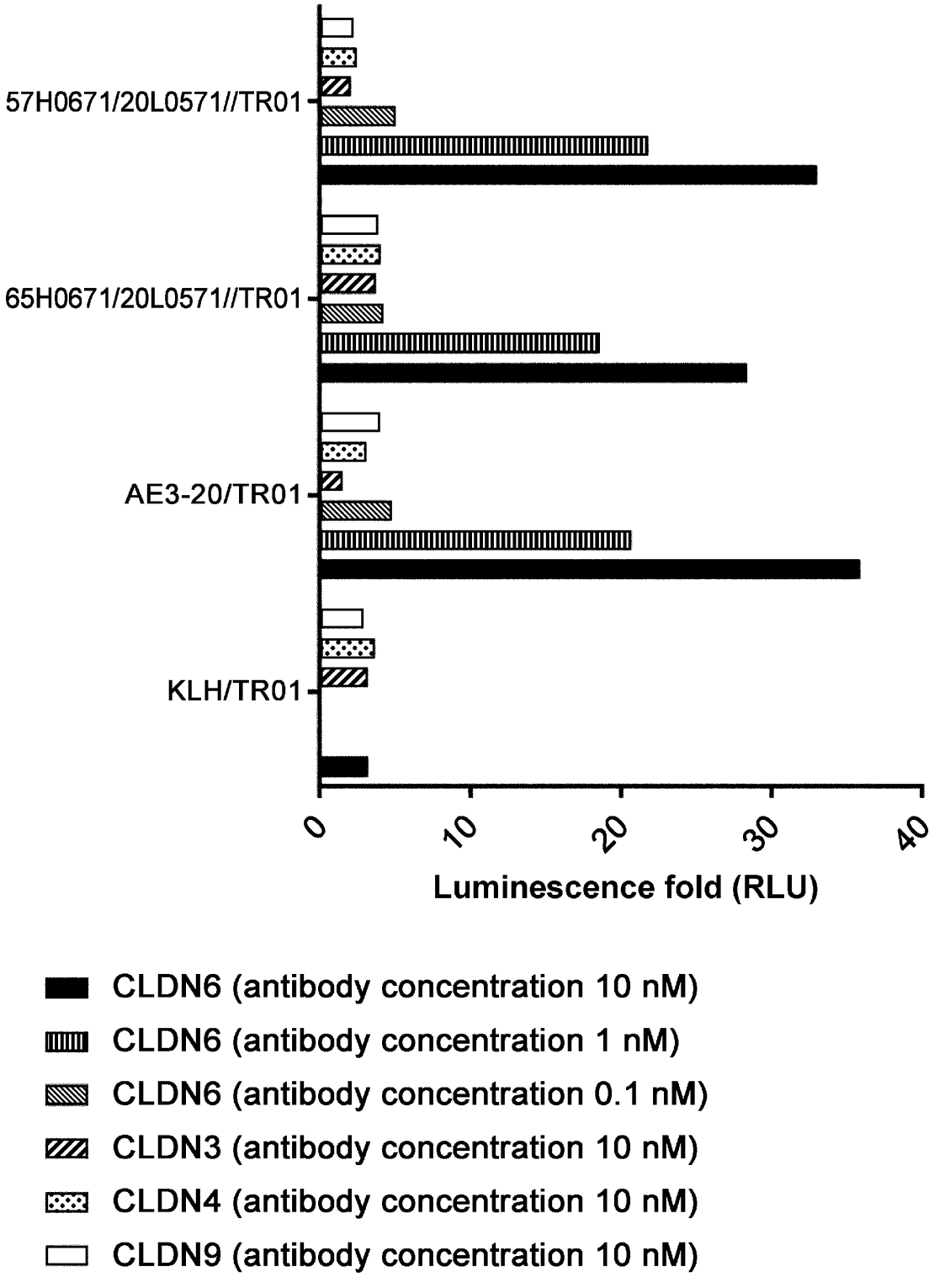

KLH/TR01
AE3-20/TR01
25H0021/20L0072//TR01
25H0024/20L0072//TR01
25H0042/20L0072//TR01
25H0176/20L0072//TR01
25H0322/20L0072//TR01
25H0562/20L0072//TR01
25H0581/20L0072//TR01
CLDN6
CLDN3
CLDN4
CLDN9
0
20
40
60
80
Luminescence fold (RLU)


KLH/TR01
AE3-20/TR01
25H/20L0532//TR01
25H0021/20L0532//TR01
25H0024/20L0532//TR01
25H0042/20L0532//TR01
25H0176/20L0532//TR01
25H0322/20L0532//TR01
25H0562/20L0532//TR01
25H0581/20L0532//TR01
CLDN6
CLDN3
CLDN4
CLDN9
0
20
40
60
80
Luminescence fold (RLU)

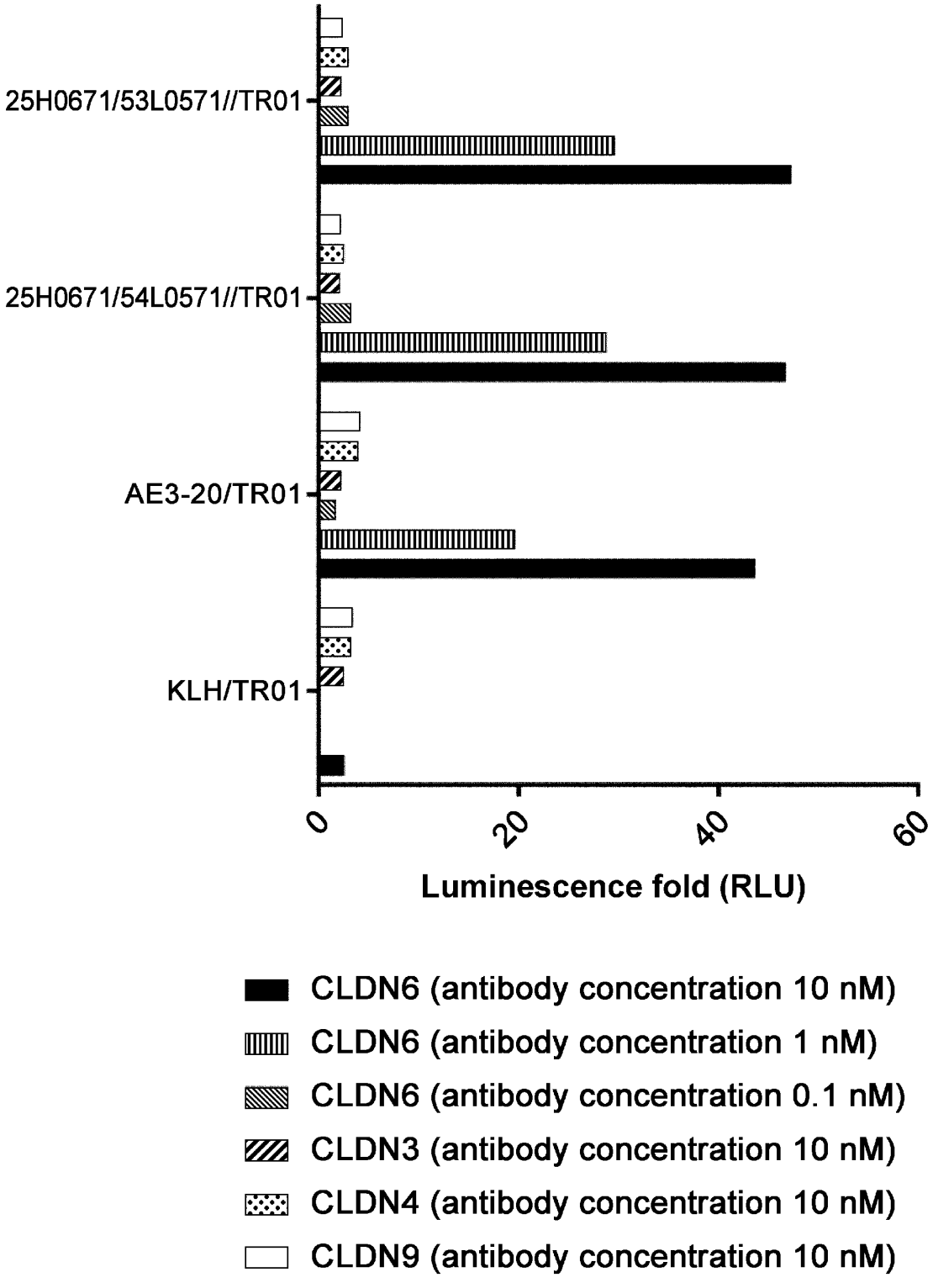
[Fig. 12]


25H0671/20L0571//TR01
AE3-20/TR01
CS2201
KLH/TR01
0
10
20
30
40
Luminescence fold (RLU)
CLDN6
CLDN3
CLDN4
CLDN9

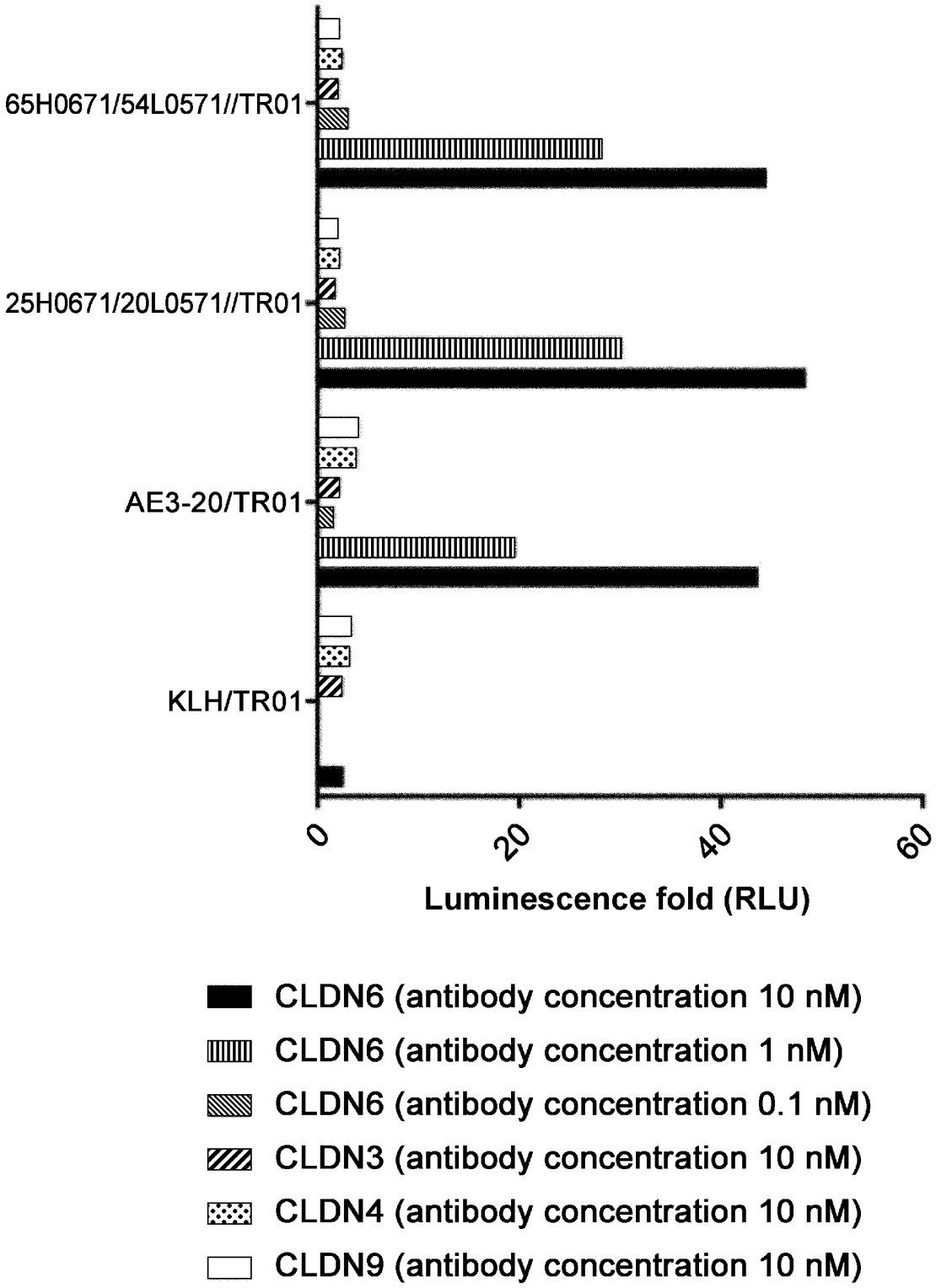
[Fig. 13]


57H0671/20L0571//TR01
65H0671/20L0571//TR01
AE3-20/TR01
KLH/TR01
0
10
20
30
40
Luminescence fold (RLU)
CLDN6 (antibody concentration 10 nM)
CLDN6 (antibody concentration 1 nM)
CLDN6 (antibody concentration 0.1 nM)
CLDN3 (antibody concentration 10 nM)
CLDN4 (antibody concentration 10 nM)
CLDN9 (antibody concentration 10 nM)

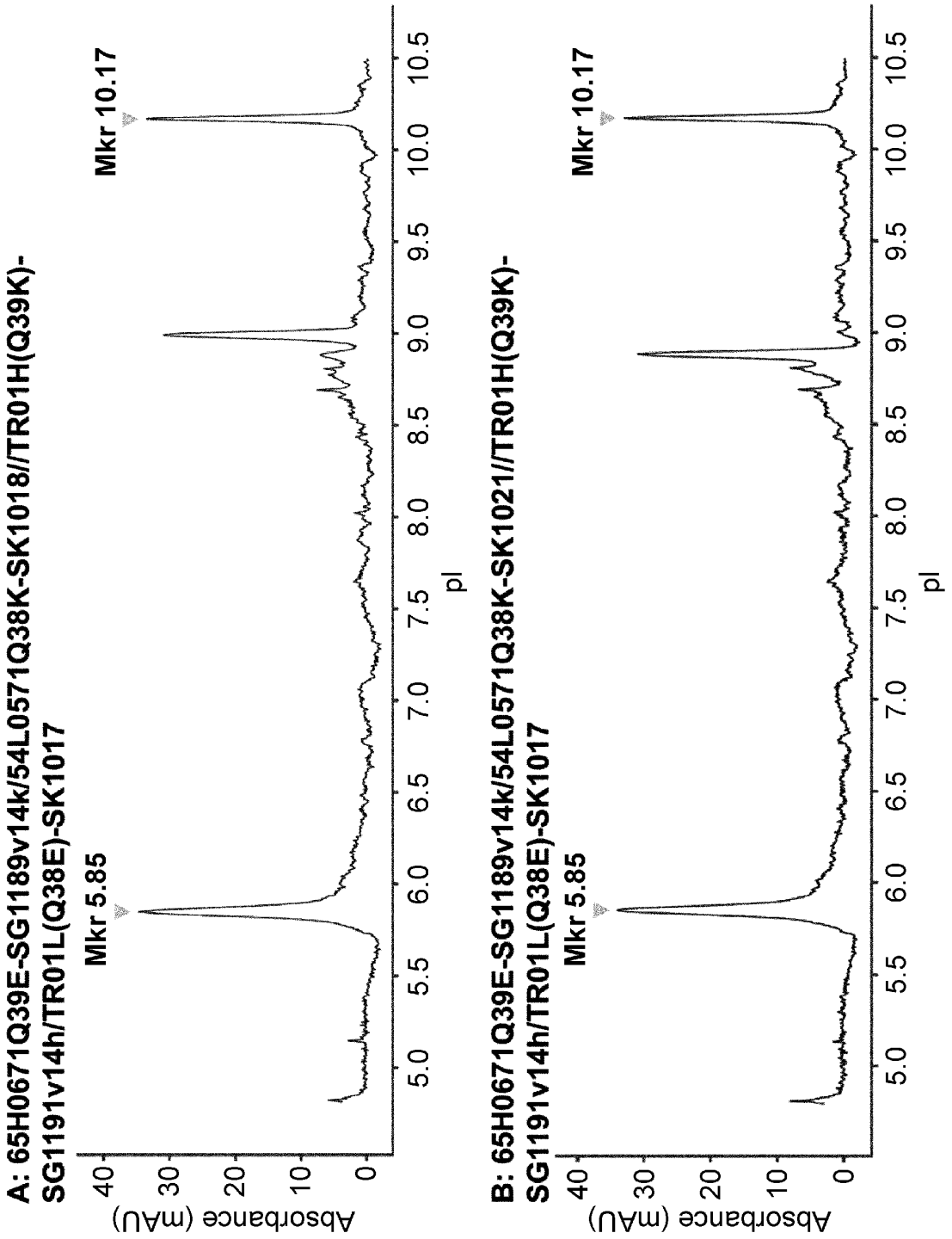
[Fig. 14]


25H0671/53L0571//TR01
25H0671/54L0571//TR01
AE3-20/TR01
KLH/TR01
0
20
40
60
Luminescence fold (RLU)
CLDN6 (antibody concentration 10 nM)
CLDN6 (antibody concentration 1 nM)
CLDN6 (antibody concentration 0.1 nM)
CLDN3 (antibody concentration 10 nM)
CLDN4 (antibody concentration 10 nM)
CLDN9 (antibody concentration 10 nM)

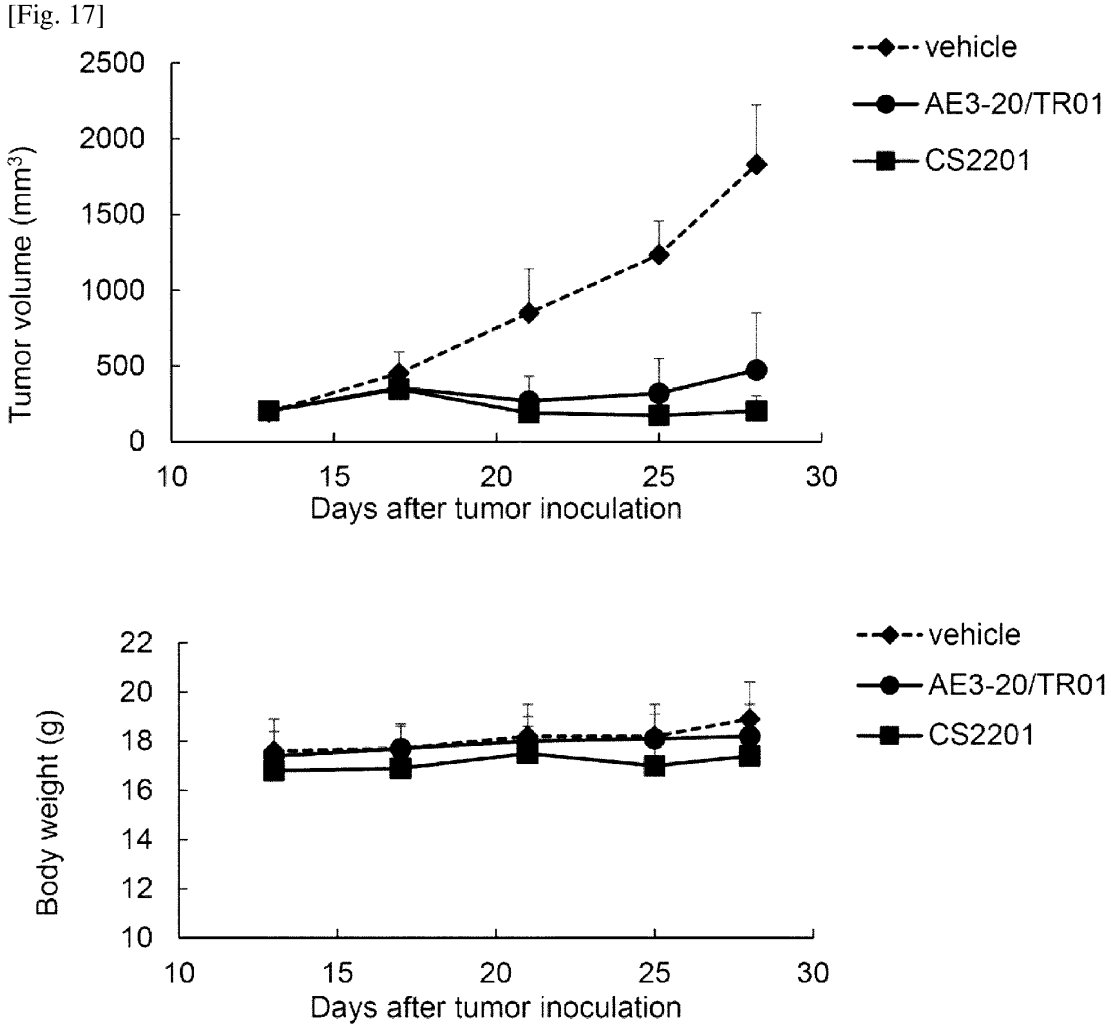
[Fig. 15]


65H0671/54L0571//TR01
25H0671/20L0571//TR01
AE3-20/TR01
KLH/TR01
0
20
40
60
Luminescence fold (RLU)
CLDN6 (antibody concentration 10 nM)
CLDN6 (antibody concentration 1 nM)
CLDN6 (antibody concentration 0.1 nM)
CLDN3 (antibody concentration 10 nM)
CLDN4 (antibody concentration 10 nM)
CLDN9 (antibody concentration 10 nM)

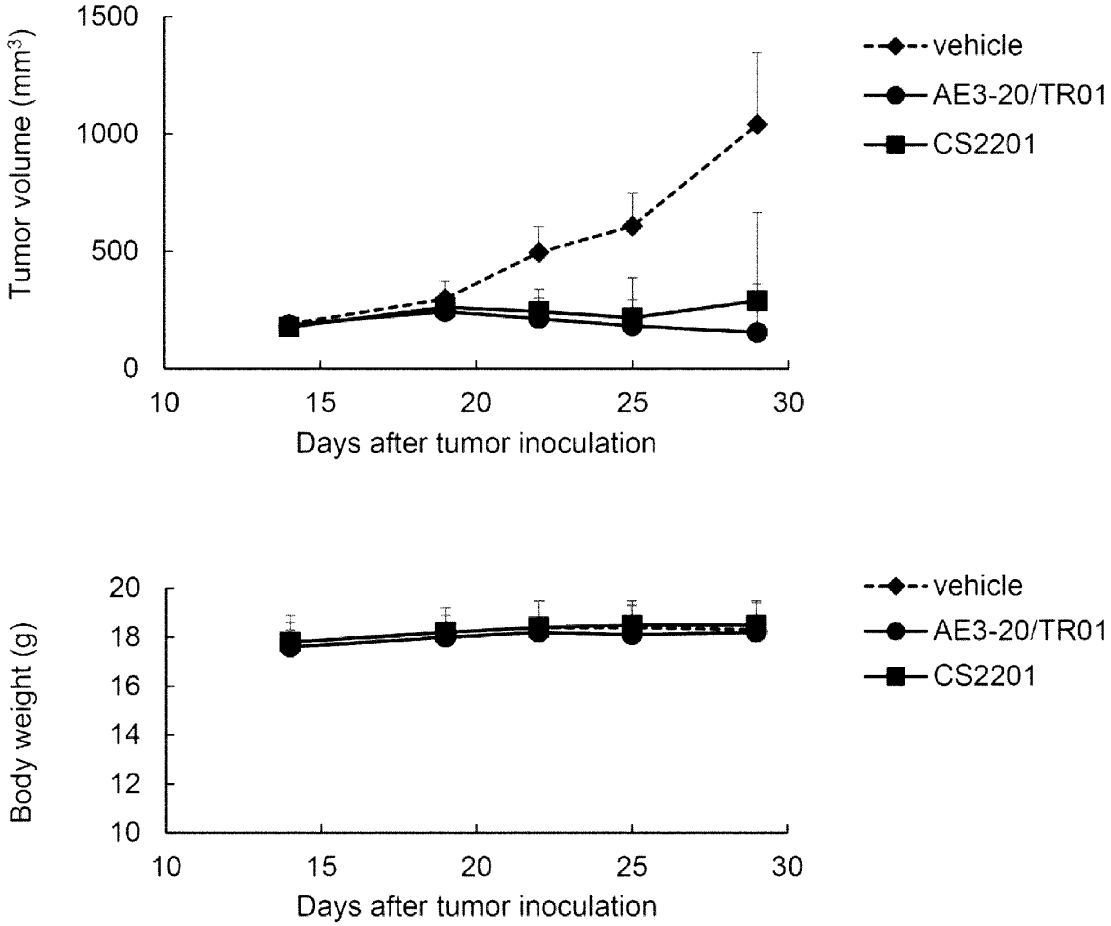
[Fig. 16]


A: 65H0671Q39E-SG1189v14k/54L0571Q38K-SK1018//TR01H(Q39K)-SG1191v14h/TR01L(Q38E)-SK1017
Mkr 5.85
Mkr 10.17
Absorbance (mAU)
pI
B: 65H0671Q39E-SG1189v14k/54L0571Q38K-SK1021//TR01H(Q39K)-SG1191v14h/TR01L(Q38E)-SK1017
Mkr 5.85
Mkr 10.17
Absorbance (mAU)
pI

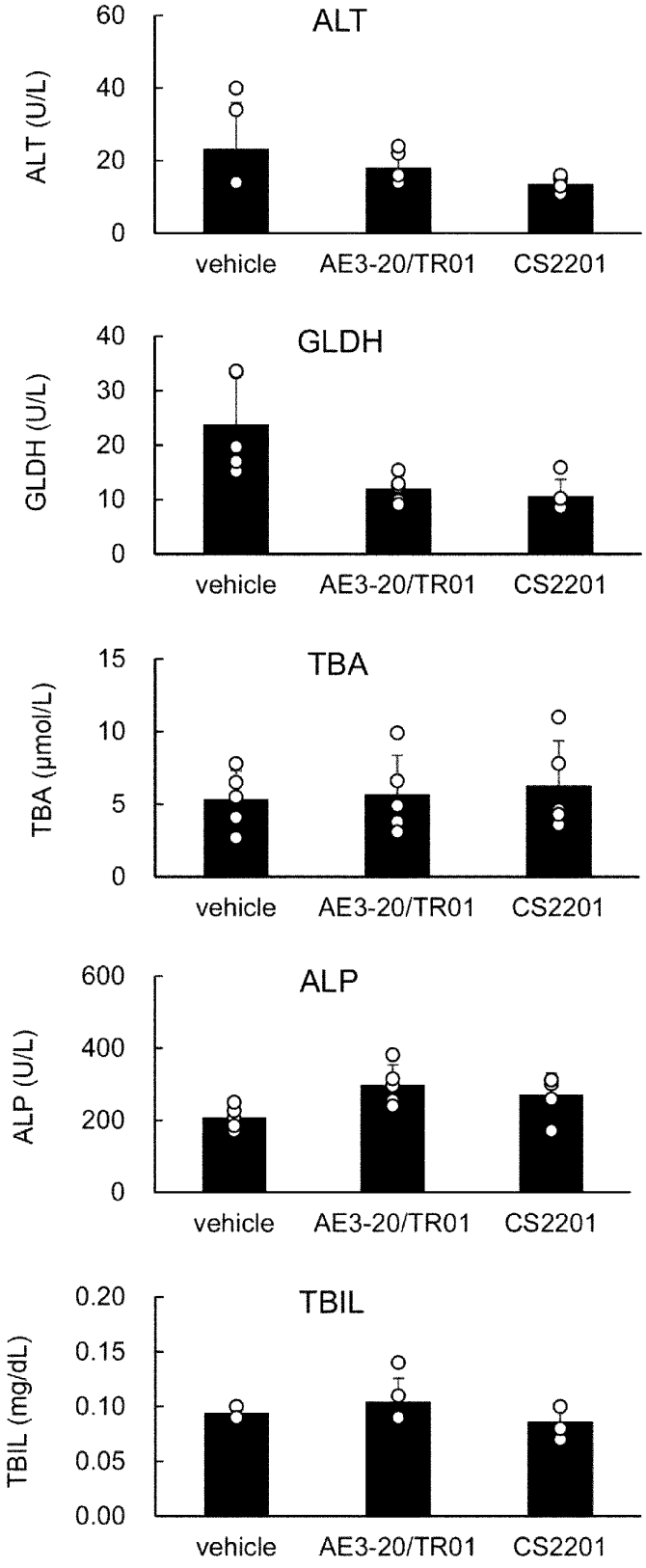
[Fig. 17]


vehicle
AE3-20/TR01
CS2201
Tumor volume (mm3)
2500
2000
1500
1000
500
0
10
15
20
25
30
Days after tumor inoculation
vehicle
AE3-20/TR01
CS2201
Body weight (g)
22
20
18
16
14
12
10
10
15
20
25
30
Days after tumor inoculation

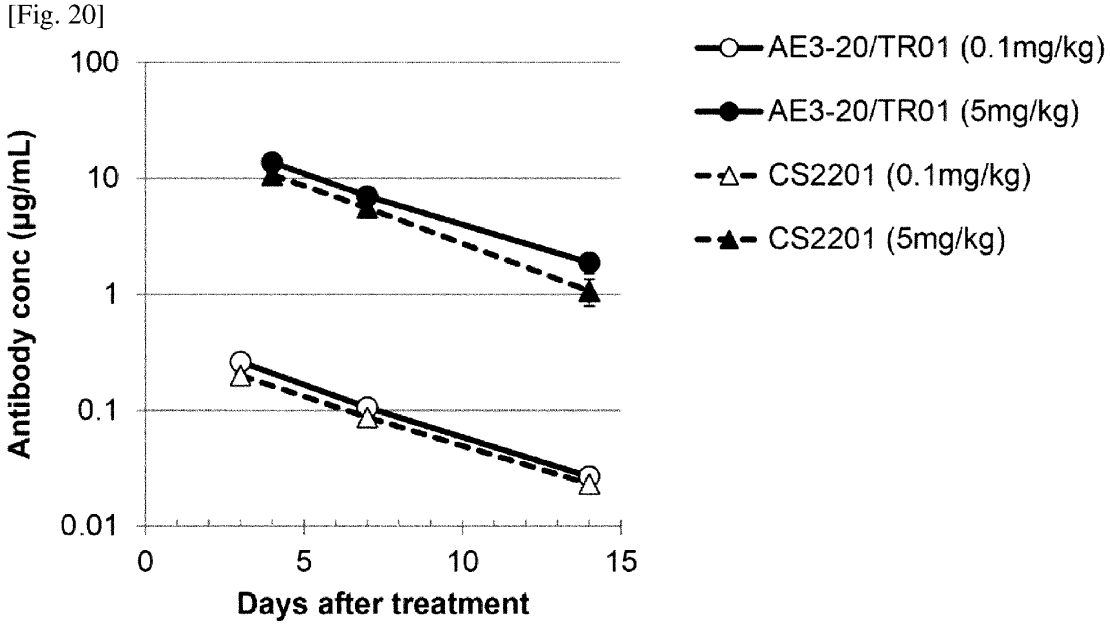
[Fig. 18]


Tumor volume (mm3)
1500
1000
500
0
10
15
20
25
30
Days after tumor inoculation
vehicle
AE3-20/TR01
CS2201
Body weight (g)
20
18
16
14
12
10
10
15
20
25
30
Days after tumor inoculation
vehicle
AE3-20/TR01
CS2201

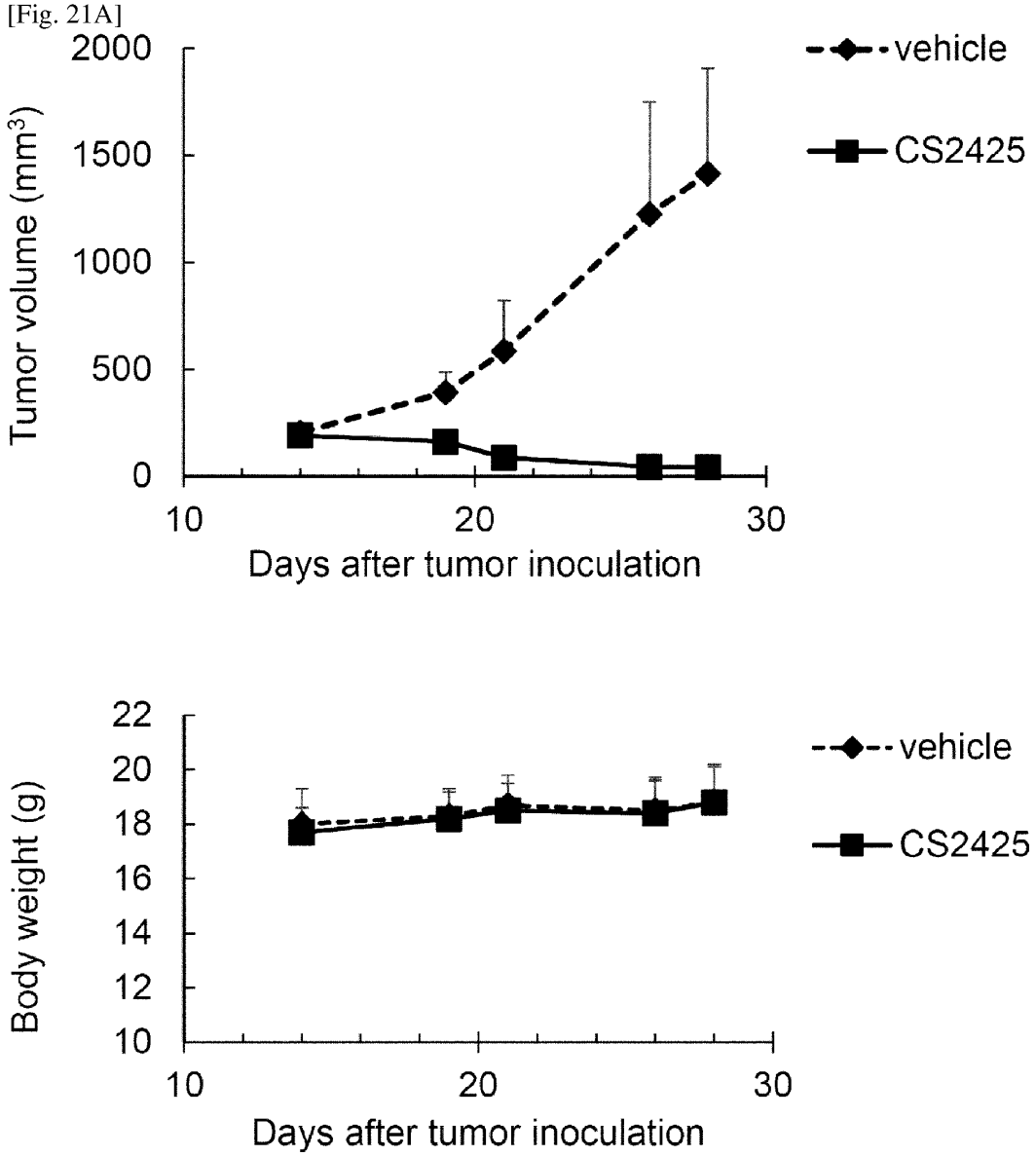
[Fig. 19]


ALT
ALT (U/L)
60
40
20
0
vehicle
AE3-20/TR01
CS2201
GLDH
GLDH (U/L)
40
30
20
10
0
vehicle
AE3-20/TR01
CS2201
TBA
TBA (μmol/L)
15
10
5
0
vehicle
AE3-20/TR01
CS2201
ALP
ALP (U/L)
600
400
200
0
vehicle
AE3-20/TR01
CS2201
TBIL
TBIL (mg/dL)
0.20
0.15
0.10
0.05
0.00
vehicle
AE3-20/TR01
CS2201

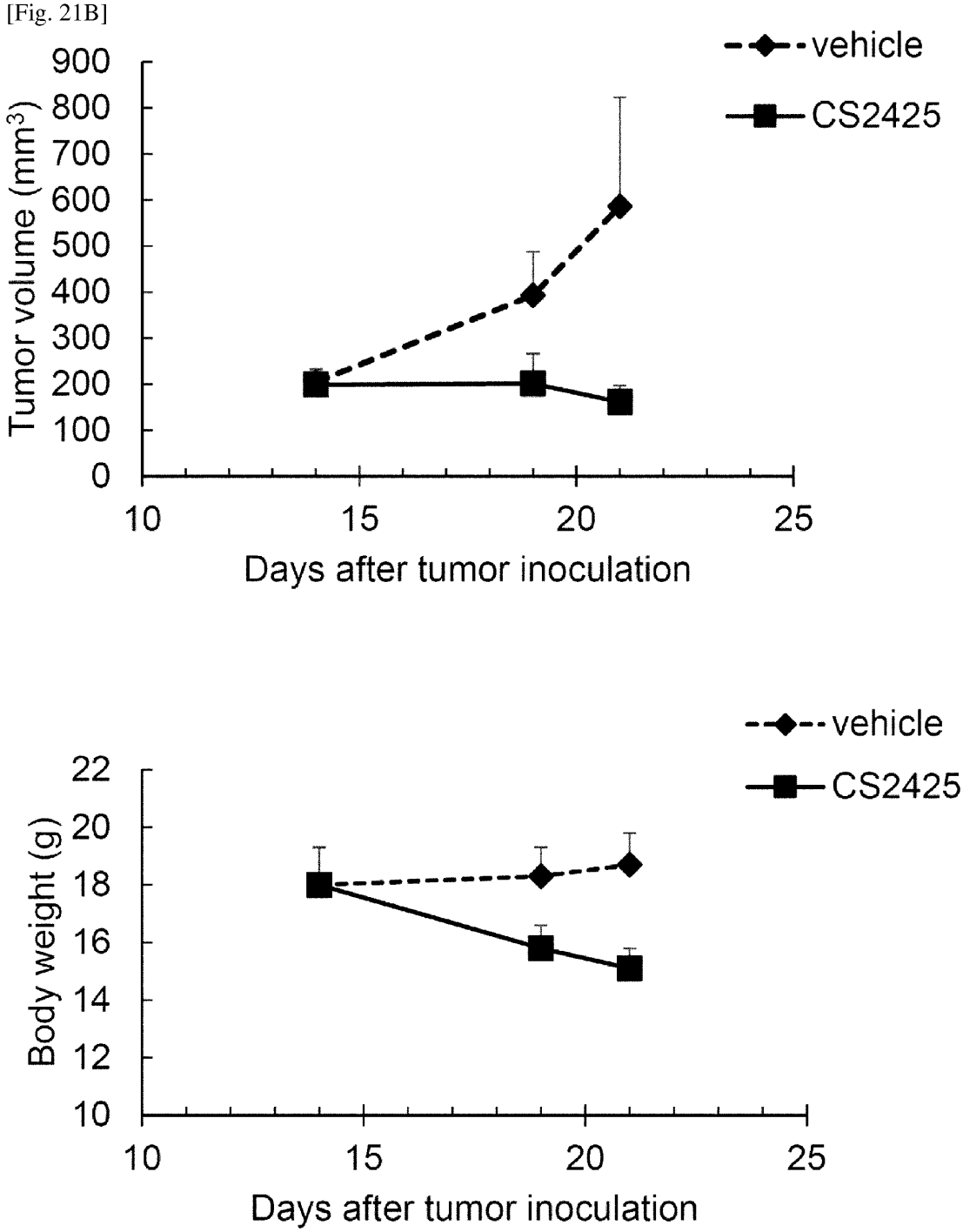
[Fig. 20]


100
10
1
0.1
0.01
Antibody conc (μg/mL)
0
5
10
15
Days after treatment
AE3-20/TR01 (0.1mg/kg)
AE3-20/TR01 (5mg/kg)
CS2201 (0.1mg/kg)
CS2201 (5mg/kg)

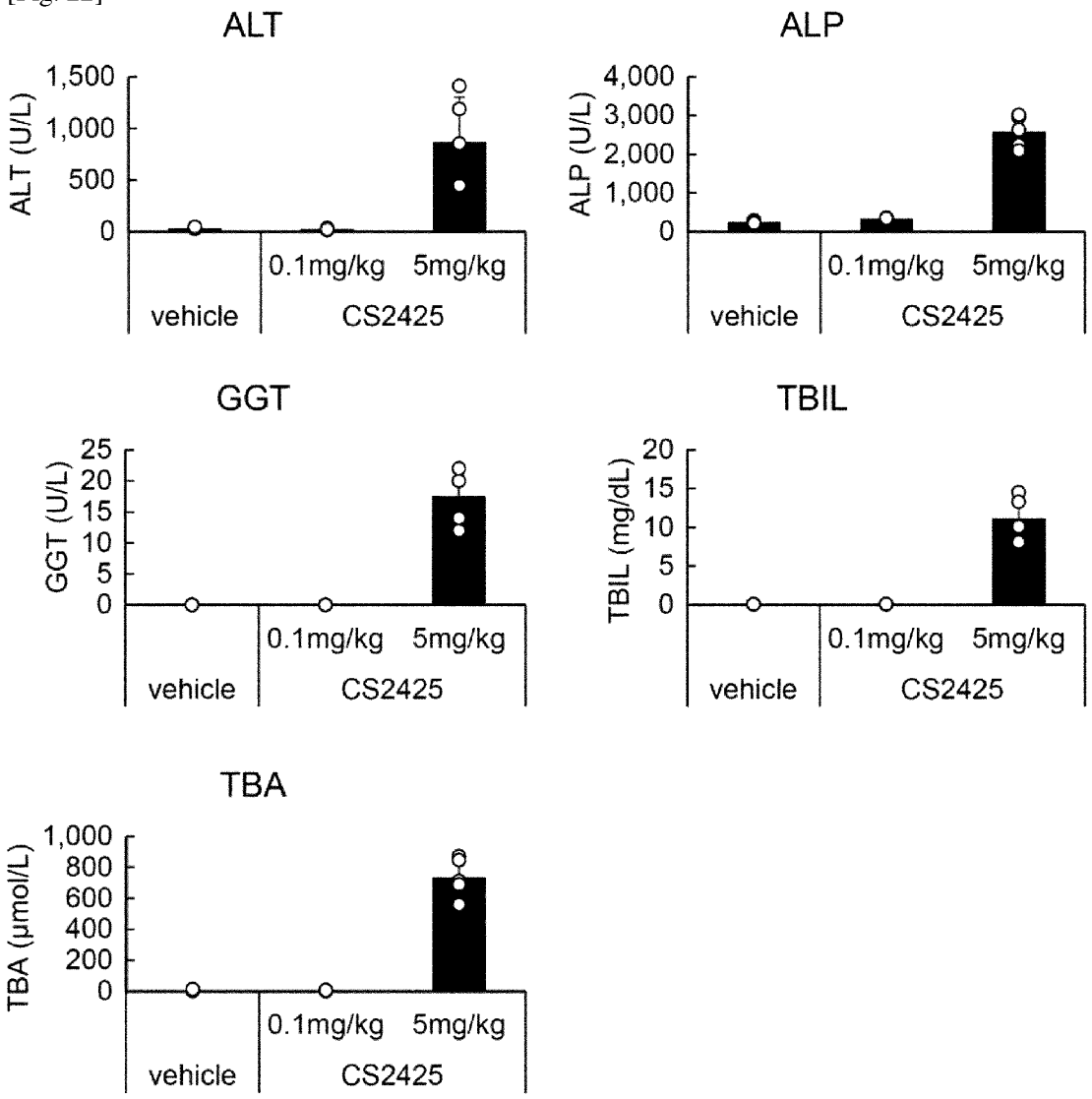
[Fig. 21A]


2000
1500
1000
500
0
Tumor volume (mm3)
10
20
30
Days after tumor inoculation
vehicle
CS2425
22
20
18
16
14
12
10
Body weight (g)
10
20
30
Days after tumor inoculation
vehicle
CS2425

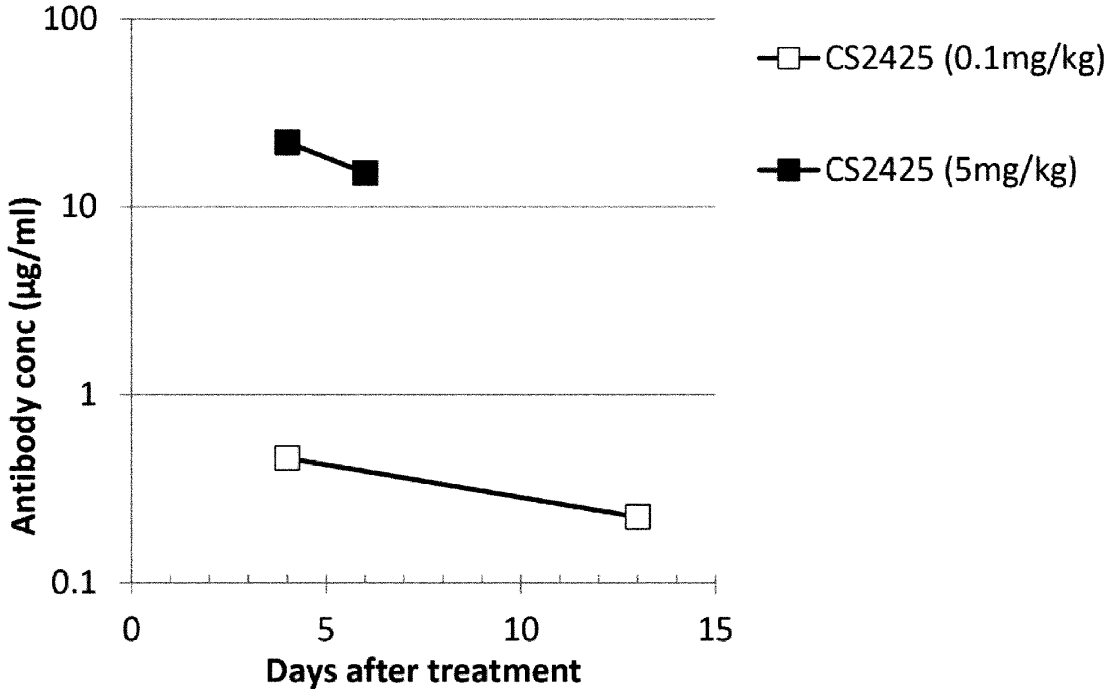
[Fig. 21B]


vehicle
CS2425
Tumor volume (mm3)
900
800
700
600
500
400
300
200
100
0
10
15
20
25
Days after tumor inoculation
vehicle
CS2425
Body weight (g)
22
20
18
16
14
12
10
10
15
20
25
Days after tumor inoculation

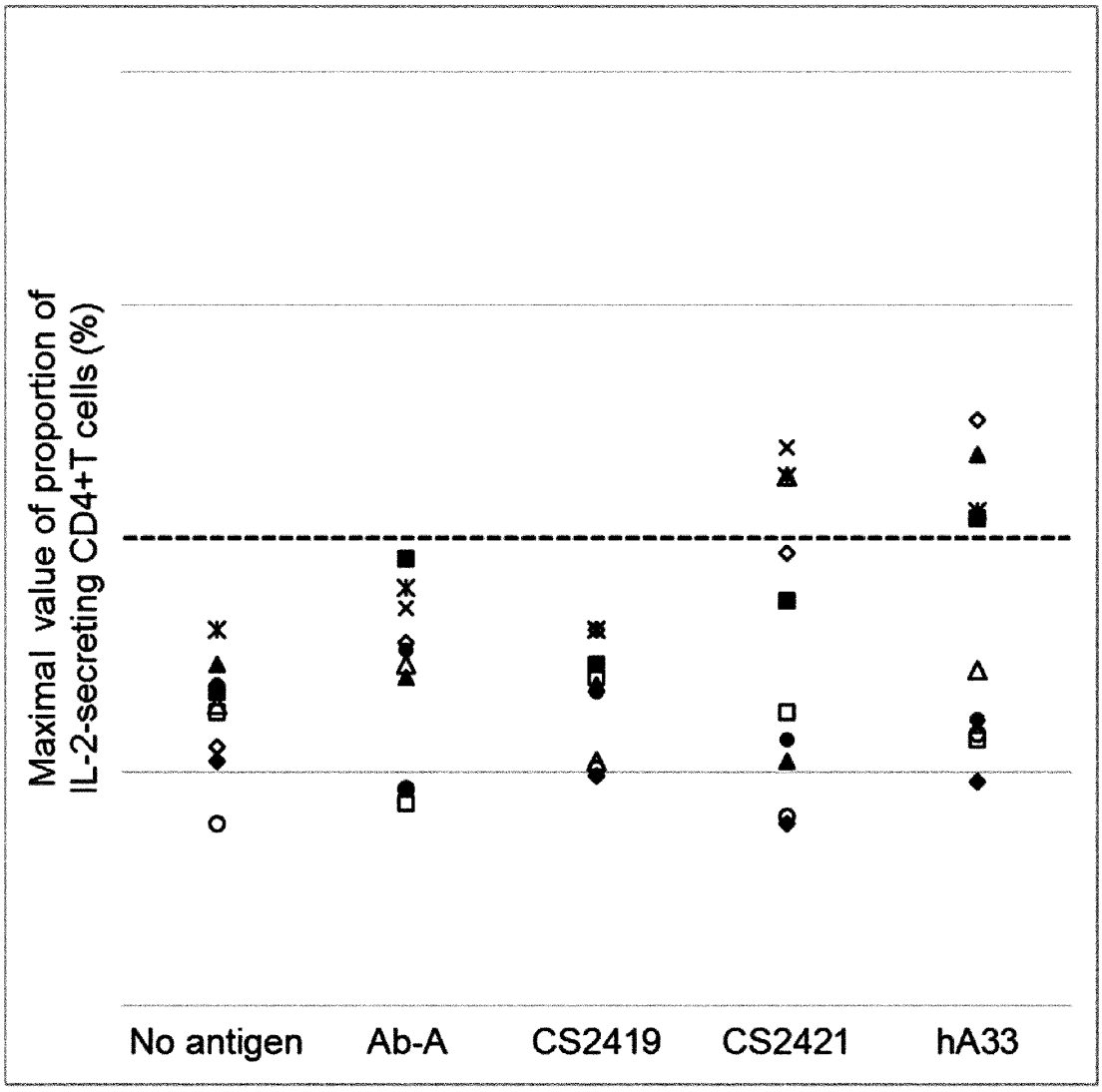
[Fig. 22]


ALT
ALT (U/L)
1,500
1,000
500
0
vehicle
0.1mg/kg
5mg/kg
CS2425
ALP
ALP (U/L)
4,000
3,000
2,000
1,000
0
vehicle
0.1mg/kg
5mg/kg
CS2425
GGT
GGT (U/L)
25
20
15
10
5
0
vehicle
0.1mg/kg
5mg/kg
CS2425
TBIL
TBIL (mg/dL)
20
15
10
5
0
vehicle
0.1mg/kg
5mg/kg
CS2425
TBA
TBA (μmol/L)
1,000
800
600
400
200
0
vehicle
0.1mg/kg
5mg/kg
CS2425

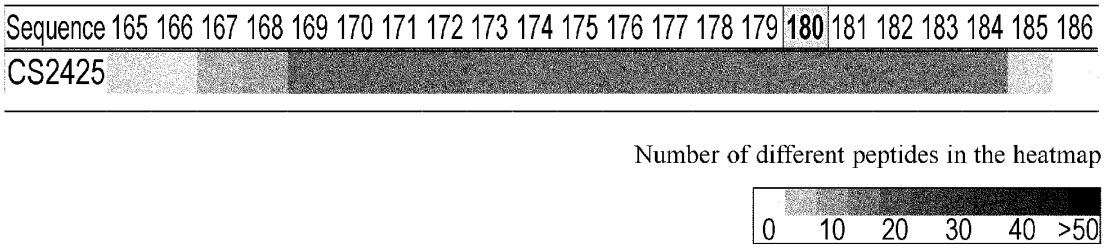
[Fig. 23]


100
10
1
0.1
Antibody conc (μg/ml)
0
5
10
15
Days after treatment
CS2425 (0.1mg/kg)
CS2425 (5mg/kg)

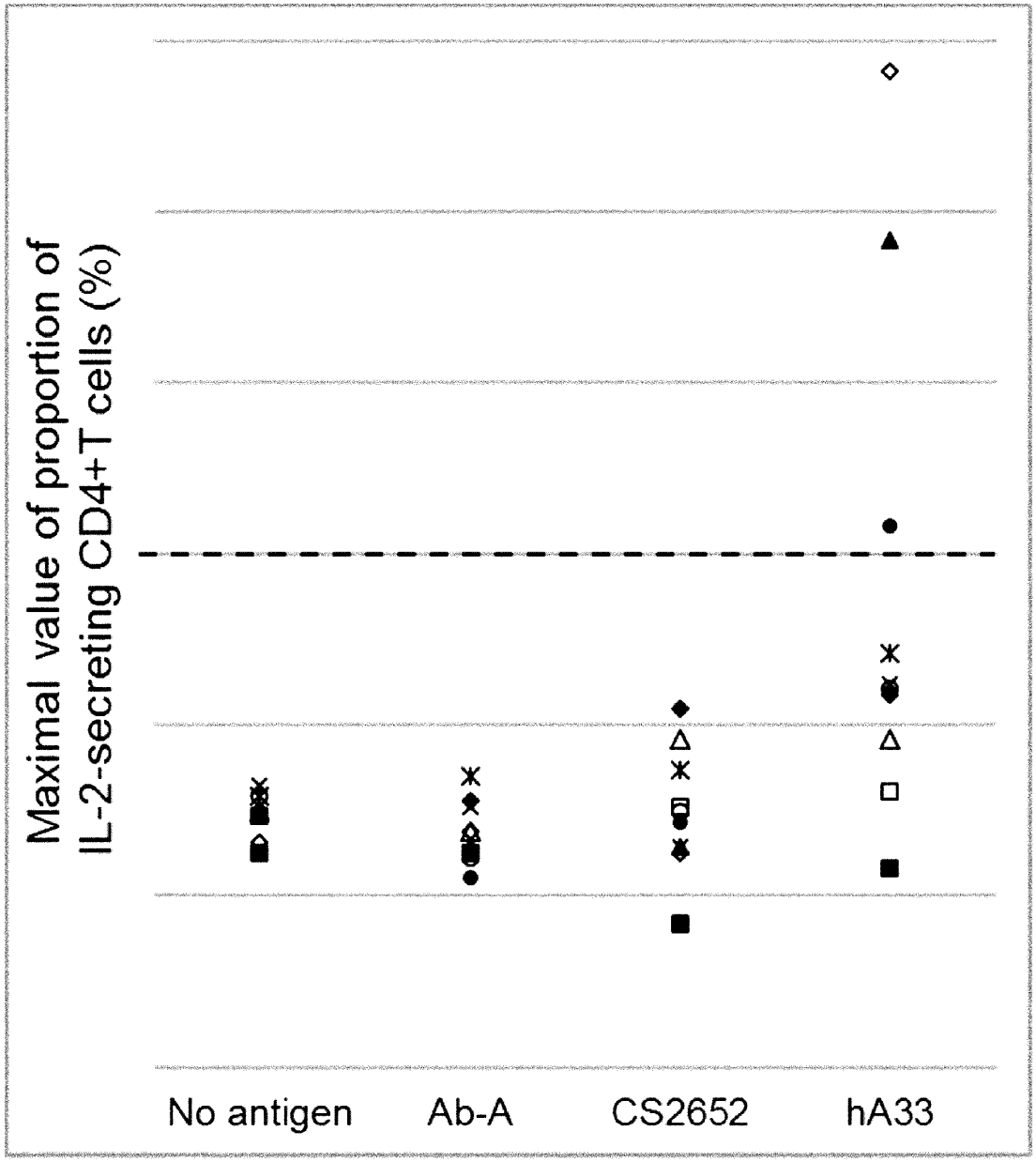
[Fig. 24]


Maximal value of proportion of IL-2-secreting CD4+T cells (%)
No antigen
Ab-A
CS2419
CS2421
hA33

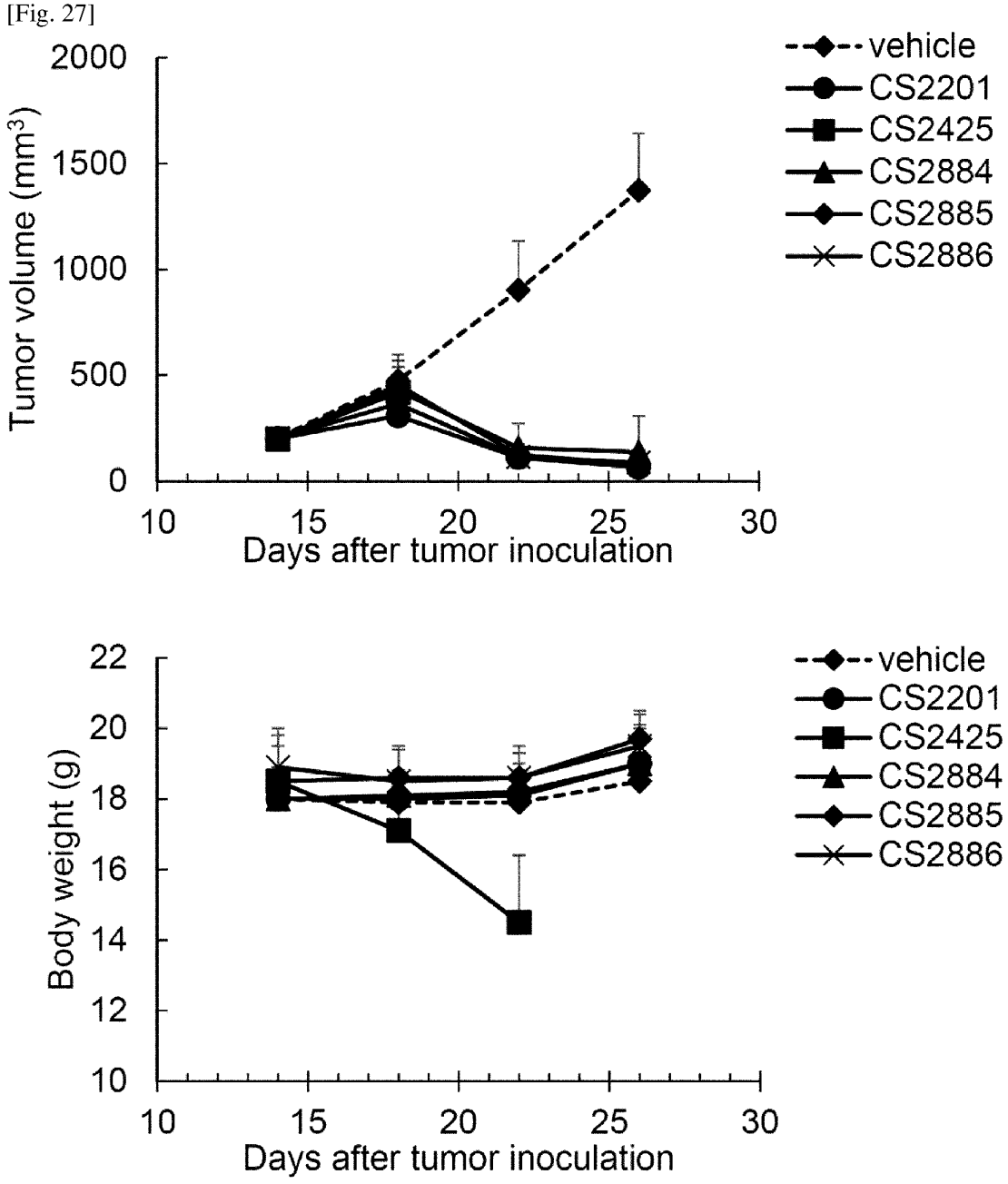
[Fig. 25]


Sequence 165 166 167 168 169 170 171 172 173 174 175 176 177 178 179 180 181 182 183 184 185 186
CS2425
Number of different peptides in the heatmap
0 10 20 30 40 >50

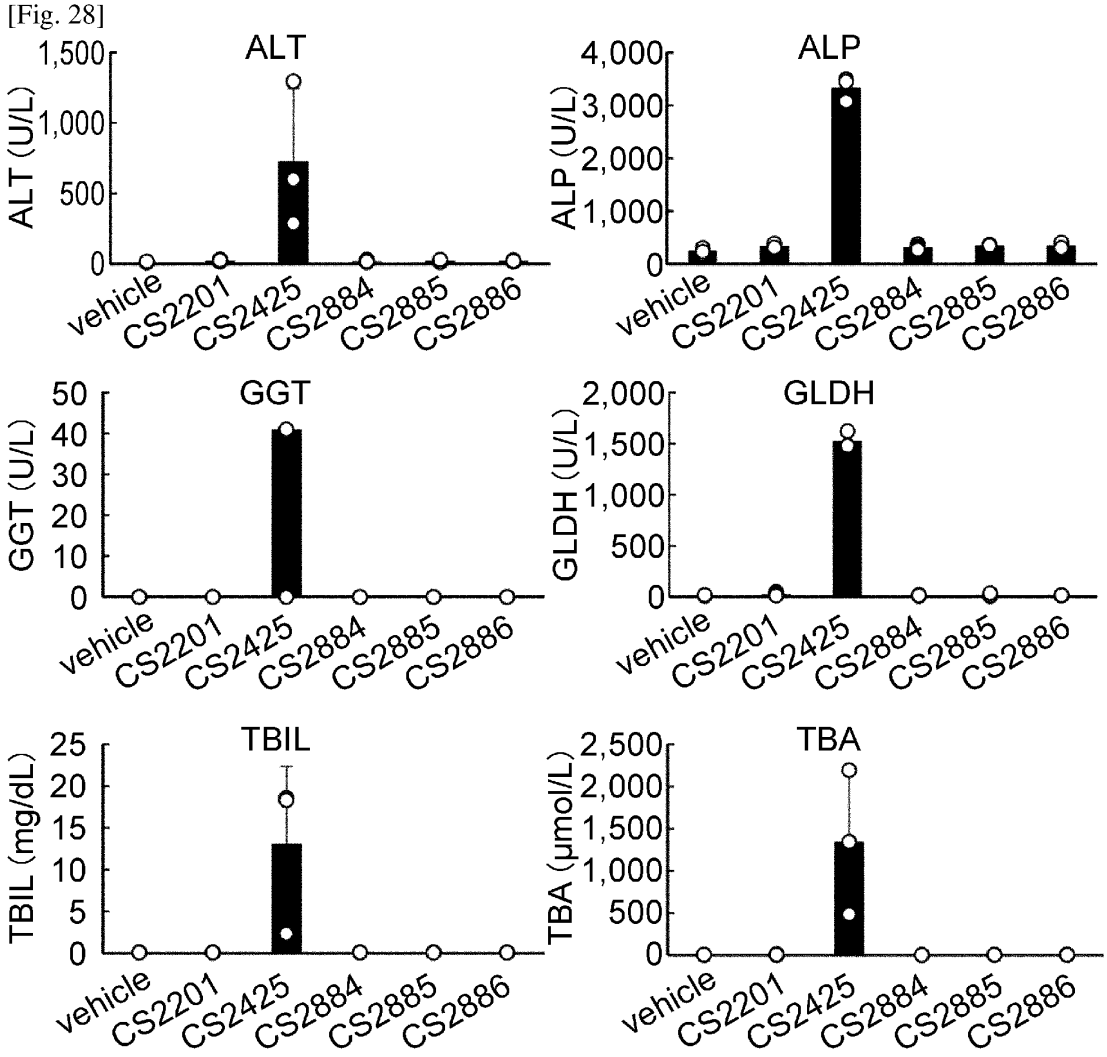
[Fig. 26]


Maximal value of proportion of IL-2-secreting CD4+T cells (%)
No antigen
Ab-A
CS2652
hA33

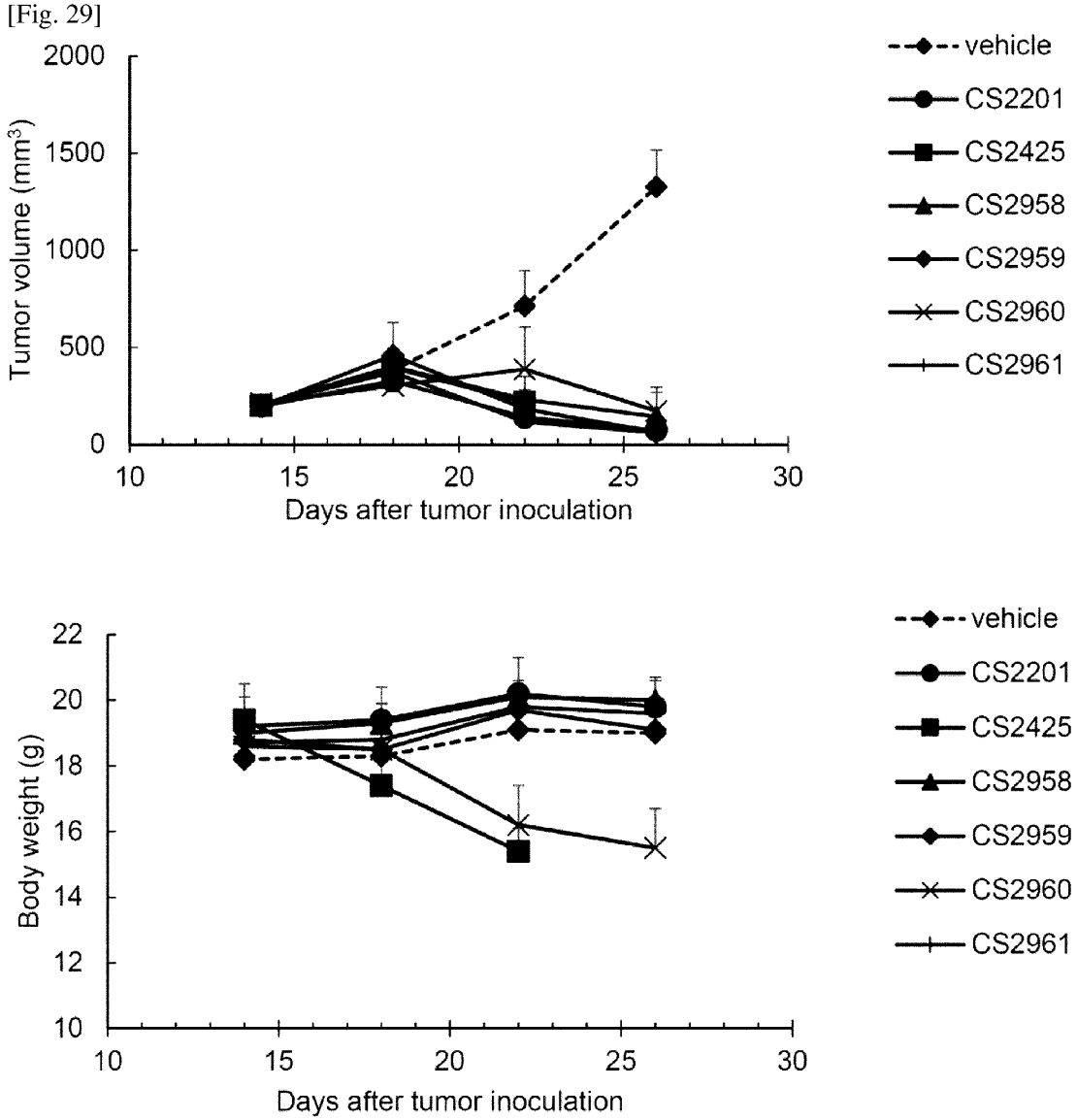
[Fig. 27]


Tumor volume (mm3)
2000
1500
1000
500
0
10
15
20
25
30
Days after tumor inoculation
vehicle
CS2201
CS2425
CS2884
CS2885
CS2886
Body weight (g)
22
20
18
16
14
12
10
10
15
20
25
30
Days after tumor inoculation
vehicle
CS2201
CS2425
CS2884
CS2885
CS2886

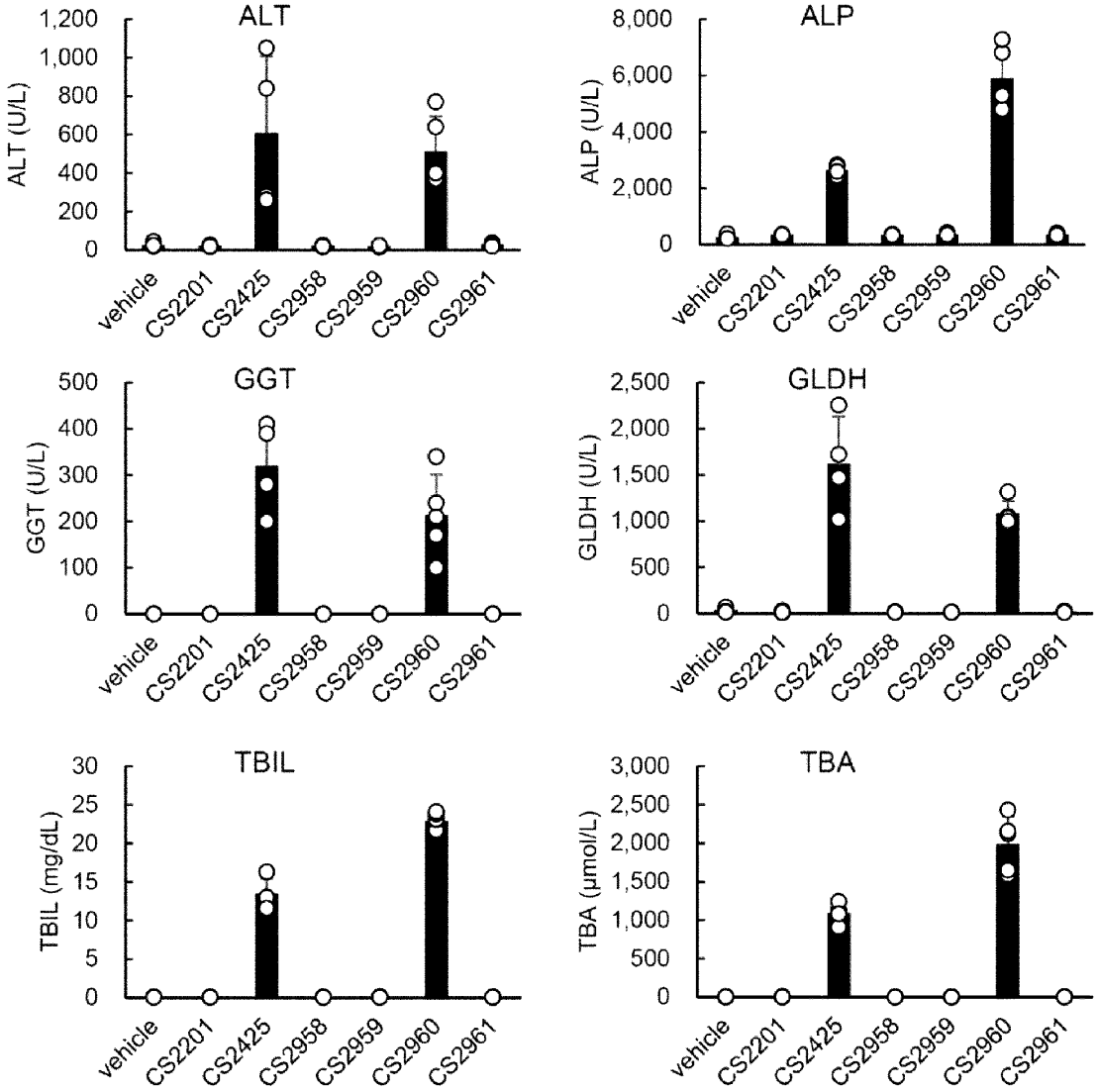
[Fig. 28]


ALT
ALT (U/L)
1,500
1,000
500
0
ALP
ALP (U/L)
4,000
3,000
2,000
1,000
0
GGT
GGT (U/L)
50
40
30
20
10
0
GLDH
GLDH (U/L)
2,000
1,500
1,000
500
0
TBIL
TBIL (mg/dL)
25
20
15
10
5
0
TBA
TBA (μmol/L)
2,500
2,000
1,500
1,000
500
0
vehicle
CS2201
CS2425
CS2884
CS2885
CS2886

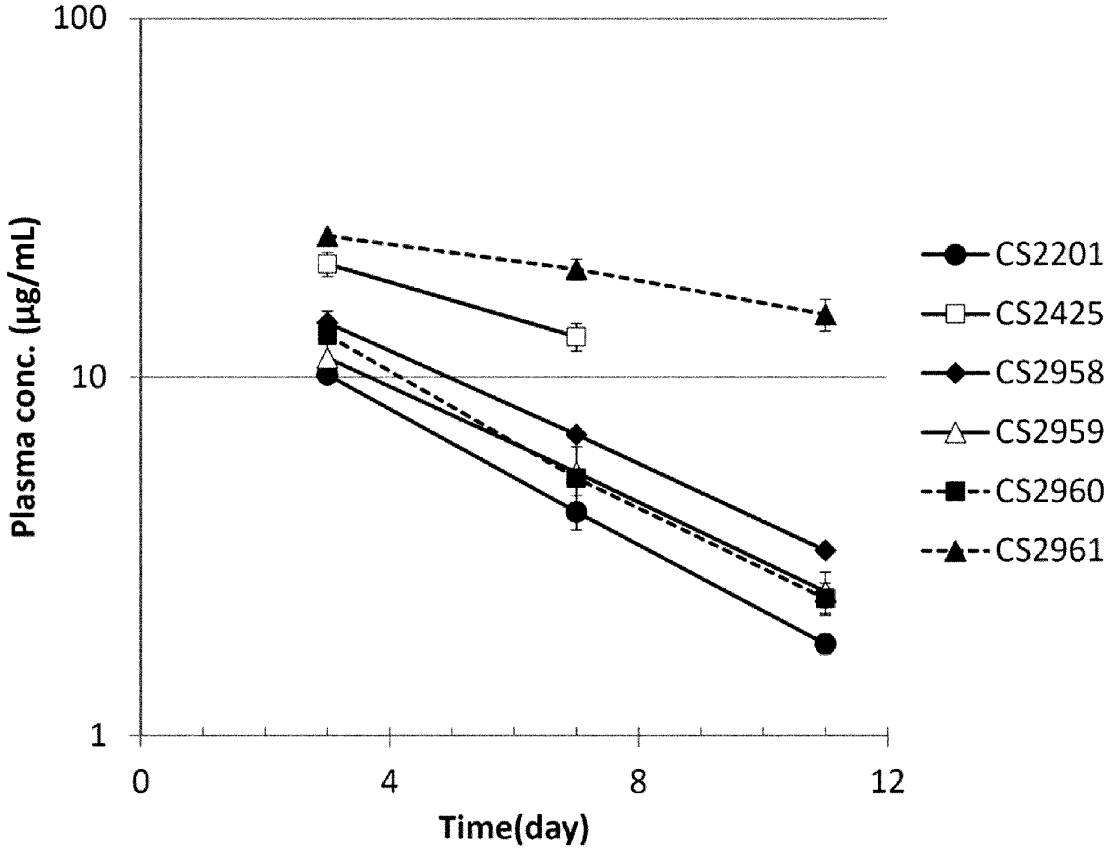
[Fig. 29]


Tumor volume (mm3)
2000
1500
1000
500
0
10
15
20
25
30
Days after tumor inoculation
vehicle
CS2201
CS2425
CS2958
CS2959
CS2960
CS2961
Body weight (g)
22
20
18
16
14
12
10
10
15
20
25
30
Days after tumor inoculation
vehicle
CS2201
CS2425
CS2958
CS2959
CS2960
CS2961

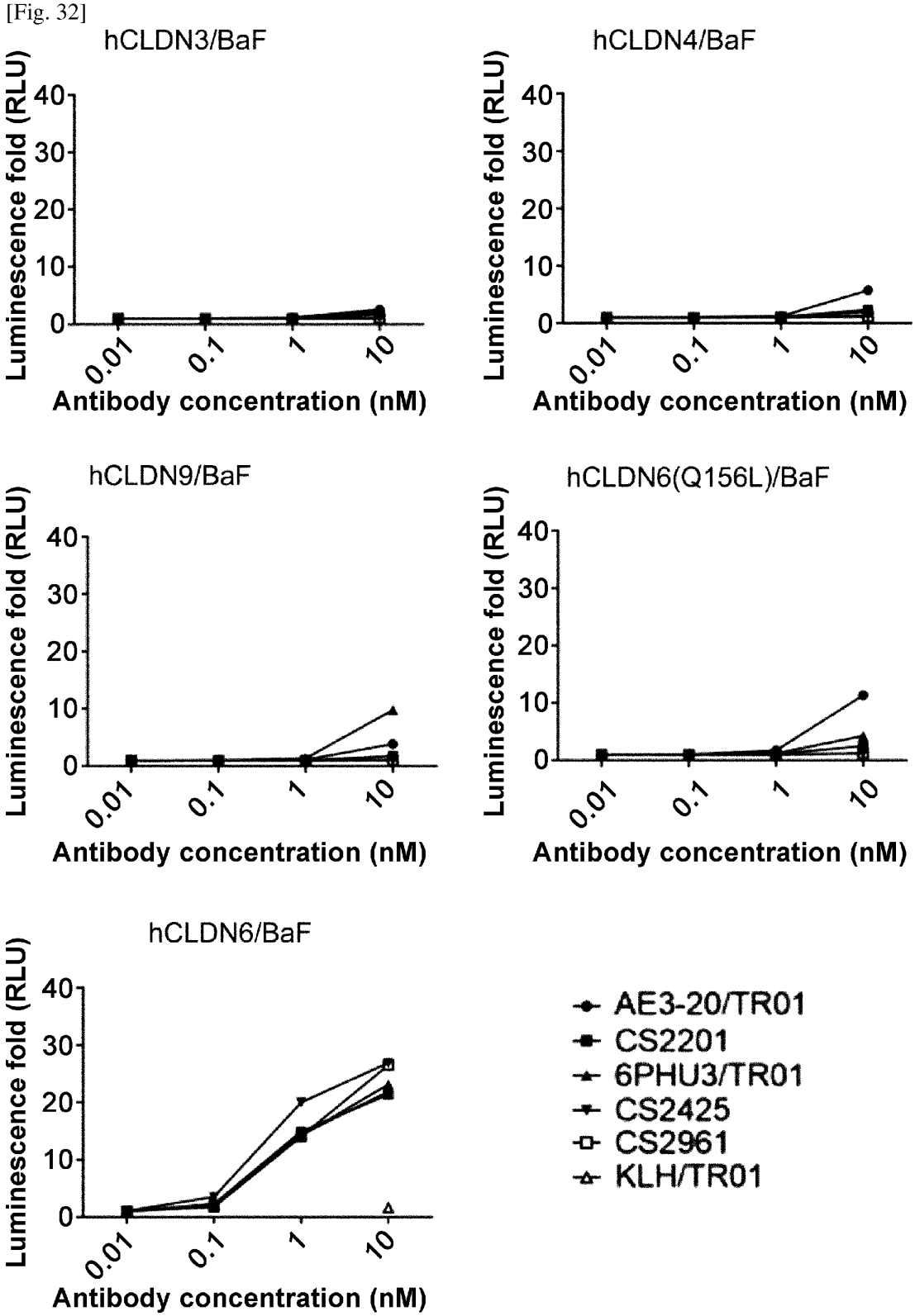
[Fig. 30]


ALT
ALT (U/L)
1,200
1,000
800
600
400
200
0
ALP
ALP (U/L)
8,000
6,000
4,000
2,000
0
GGT
GGT (U/L)
500
400
300
200
100
0
GLDH
GLDH (U/L)
2,500
2,000
1,500
1,000
500
0
TBIL
TBIL (mg/dL)
30
25
20
15
10
5
0
TBA
TBA (μmol/L)
3,000
2,500
2,000
1,500
1,000
500
0
vehicle
CS2201
CS2425
CS2958
CS2959
CS2960
CS2961

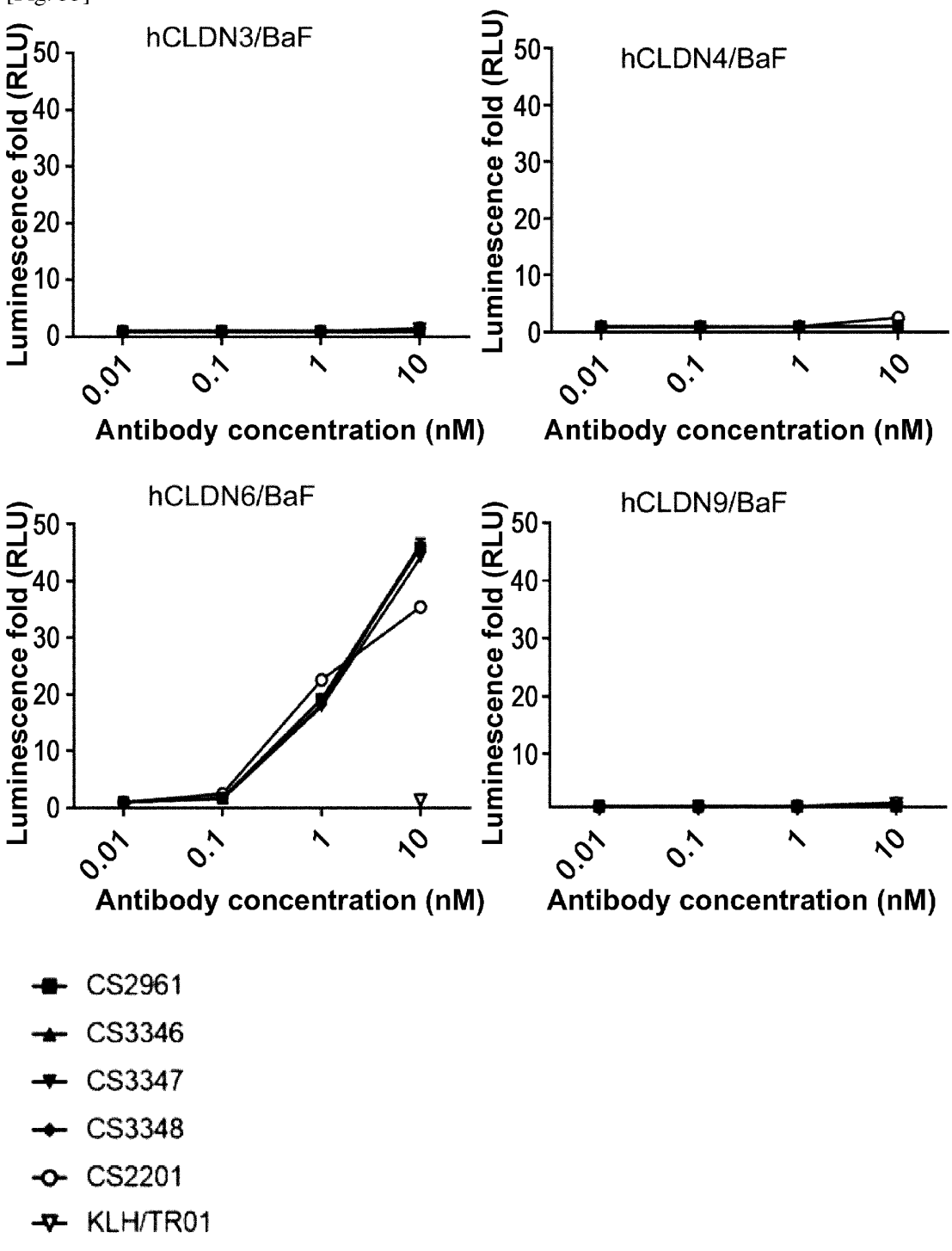
[Fig. 31]


100
10
1
Plasma conc. (μg/mL)
0
4
8
12
Time(day)
CS2201
CS2425
CS2958
CS2959
CS2960
CS2961

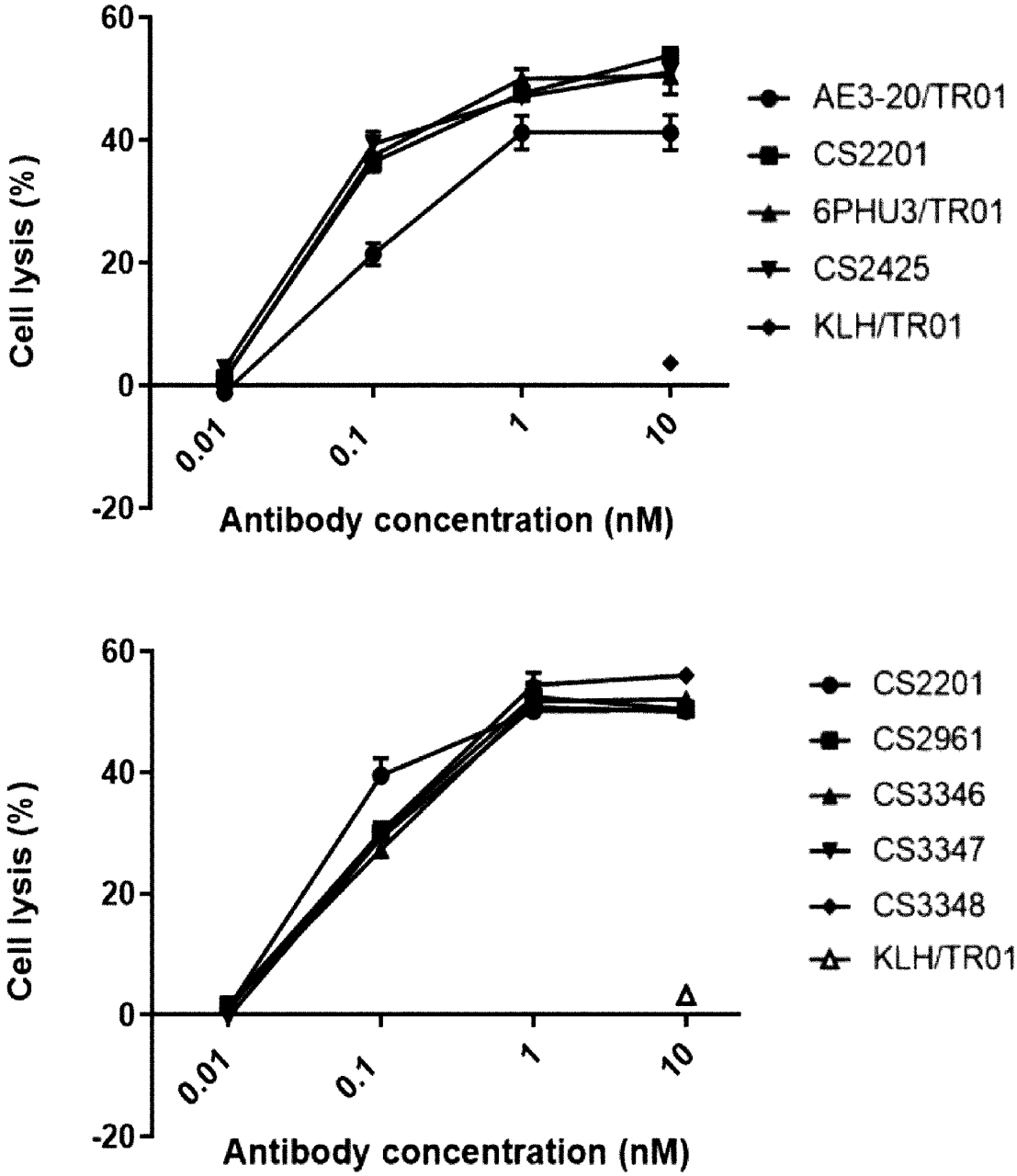
[Fig. 32]


hCLDN3/BaF
hCLDN4/BaF
hCLDN9/BaF
hCLDN6(Q156L)/BaF
hCLDN6/BaF
Luminescence fold (RLU)
Antibody concentration (nM)
0
10
20
30
40
0.01
0.1
1
10
AE3-20/TR01
CS2201
6PHU3/TR01
CS2425
CS2961
KLH/TR01

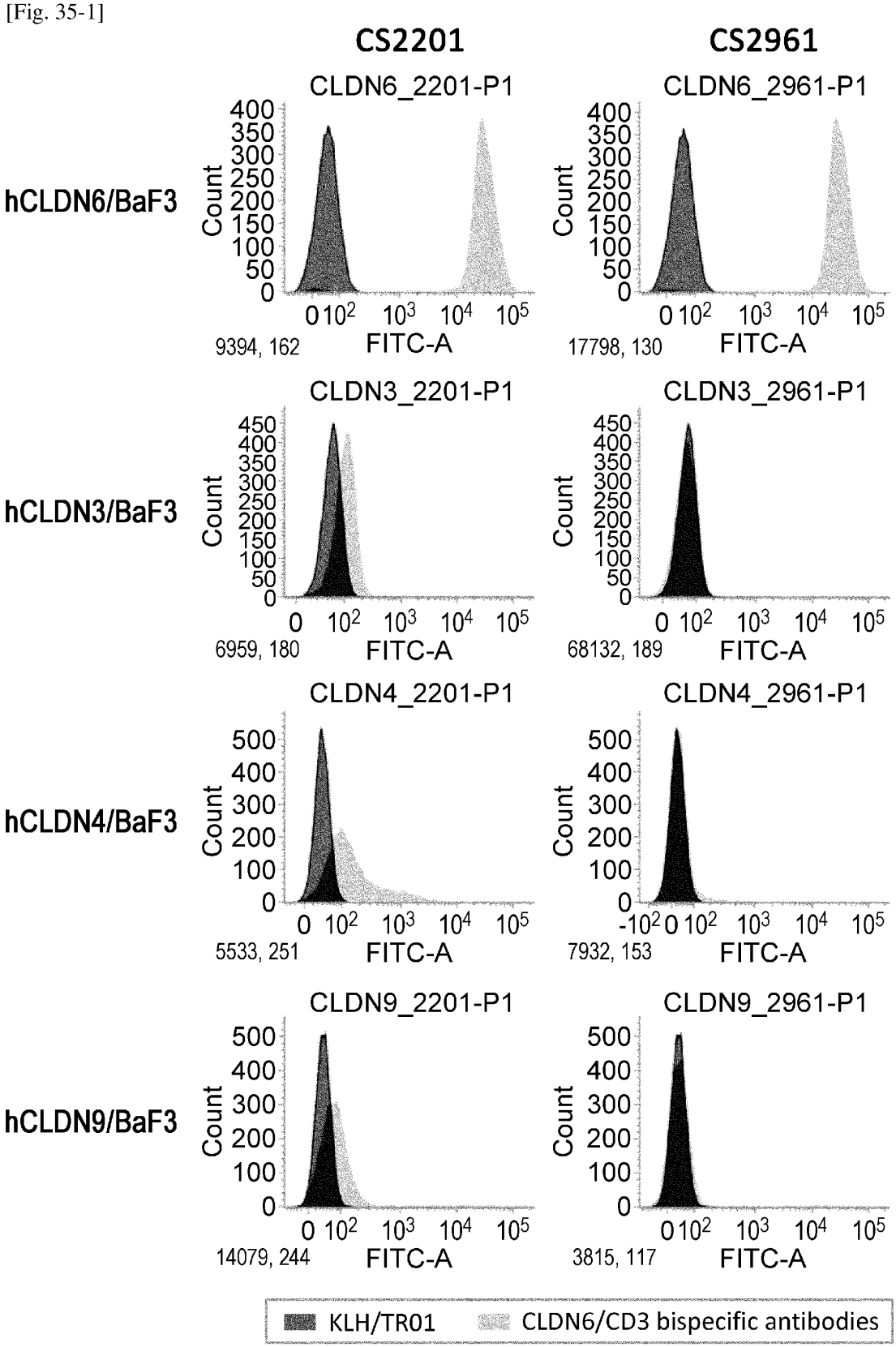
[Fig. 33]


hCLDN3/BaF
hCLDN4/BaF
hCLDN6/BaF
hCLDN9/BaF
Luminescence fold (RLU)
0
10
20
30
40
50
0.01
0.1
1
10
Antibody concentration (nM)
CS2961
CS3346
CS3347
CS3348
CS2201
KLH/TR01

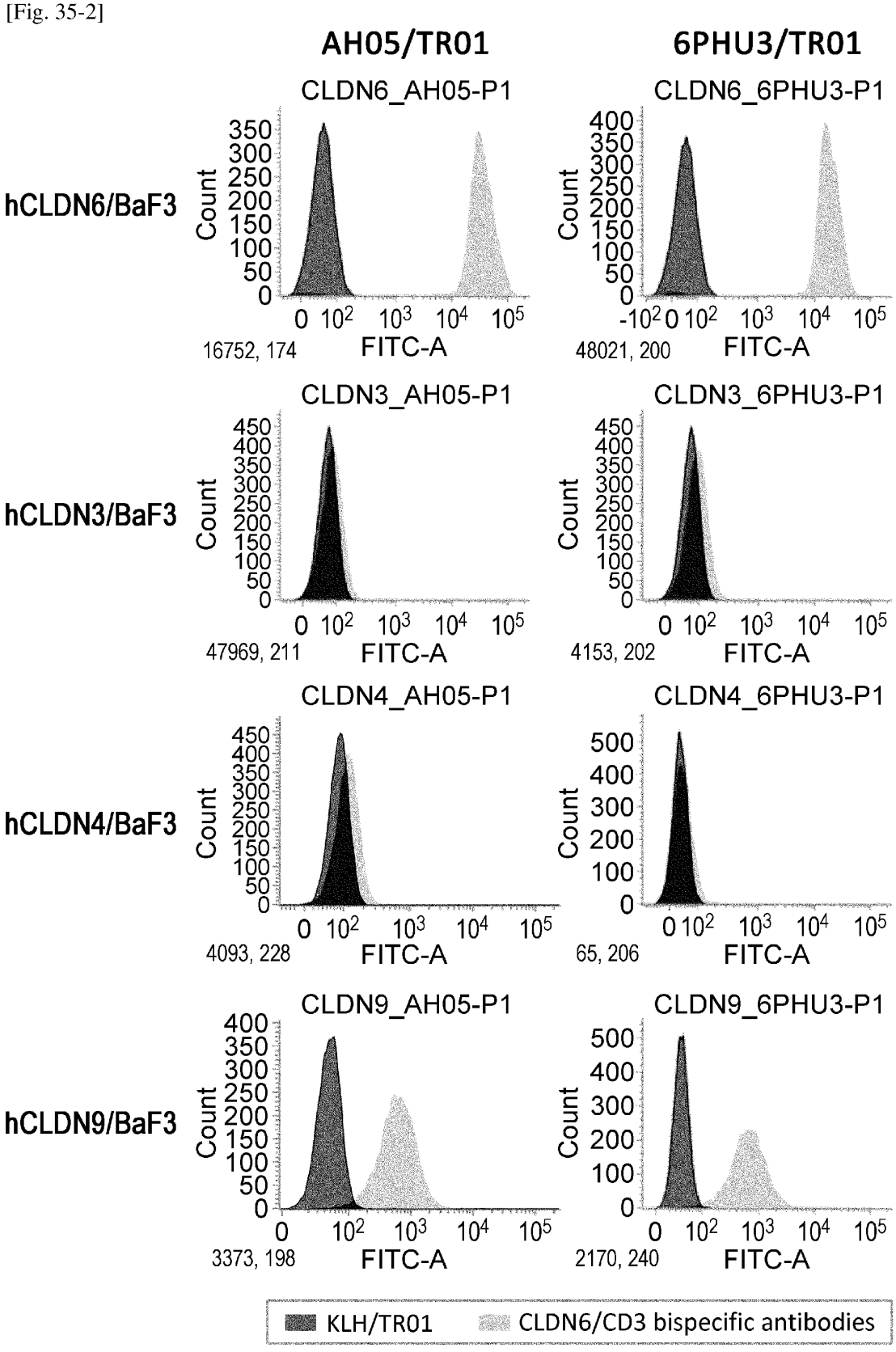
[Fig. 34]


60
40
20
0
-20
Cell lysis (%)
0.01
0.1
1
10
Antibody concentration (nM)
AE3-20/TR01
CS2201
6PHU3/TR01
CS2425
KLH/TR01
60
40
20
0
-20
Cell lysis (%)
0.01
0.1
1
10
Antibody concentration (nM)
CS2201
CS2961
CS3346
CS3347
CS3348
KLH/TR01

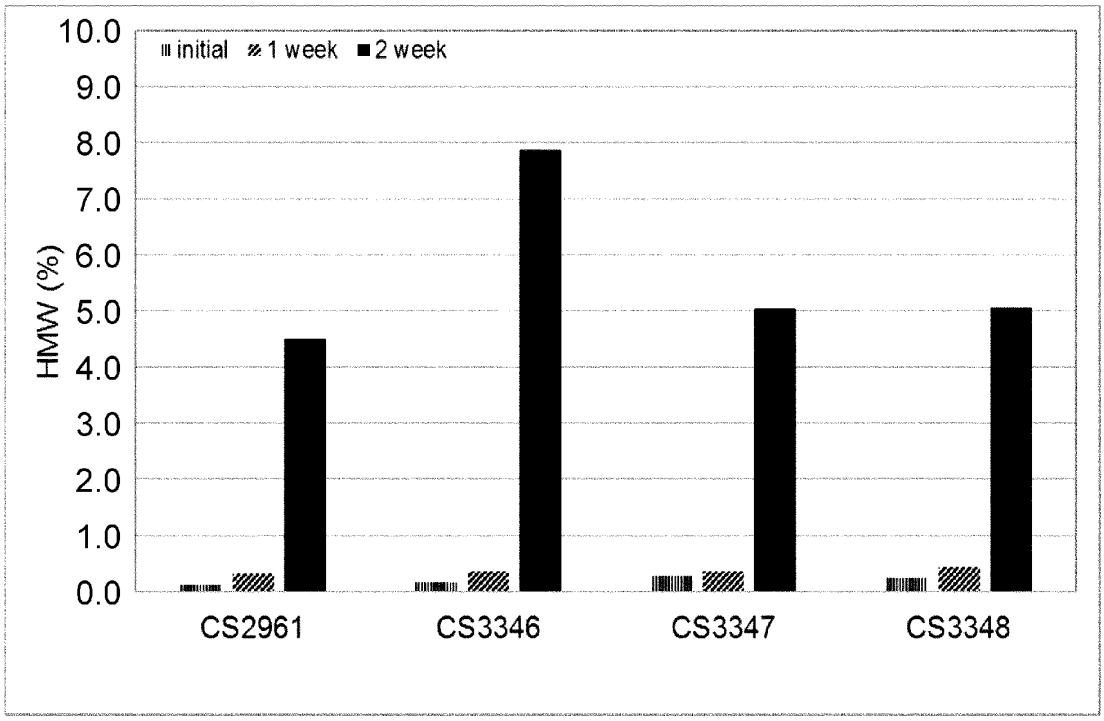
[Fig. 35-1]


CS2201
CS2961
hCLDN6/BaF3
hCLDN3/BaF3
hCLDN4/BaF3
hCLDN9/BaF3
CLDN6_2201-P1
CLDN6_2961-P1
CLDN3_2201-P1
CLDN3_2961-P1
CLDN4_2201-P1
CLDN4_2961-P1
CLDN9_2201-P1
CLDN9_2961-P1
Count
FITC-A
9394, 162
17798, 130
6959, 180
68132, 189
5533, 251
7932, 153
14079, 244
3815, 117
KLH/TR01
CLDN6/CD3 bispecific antibodies

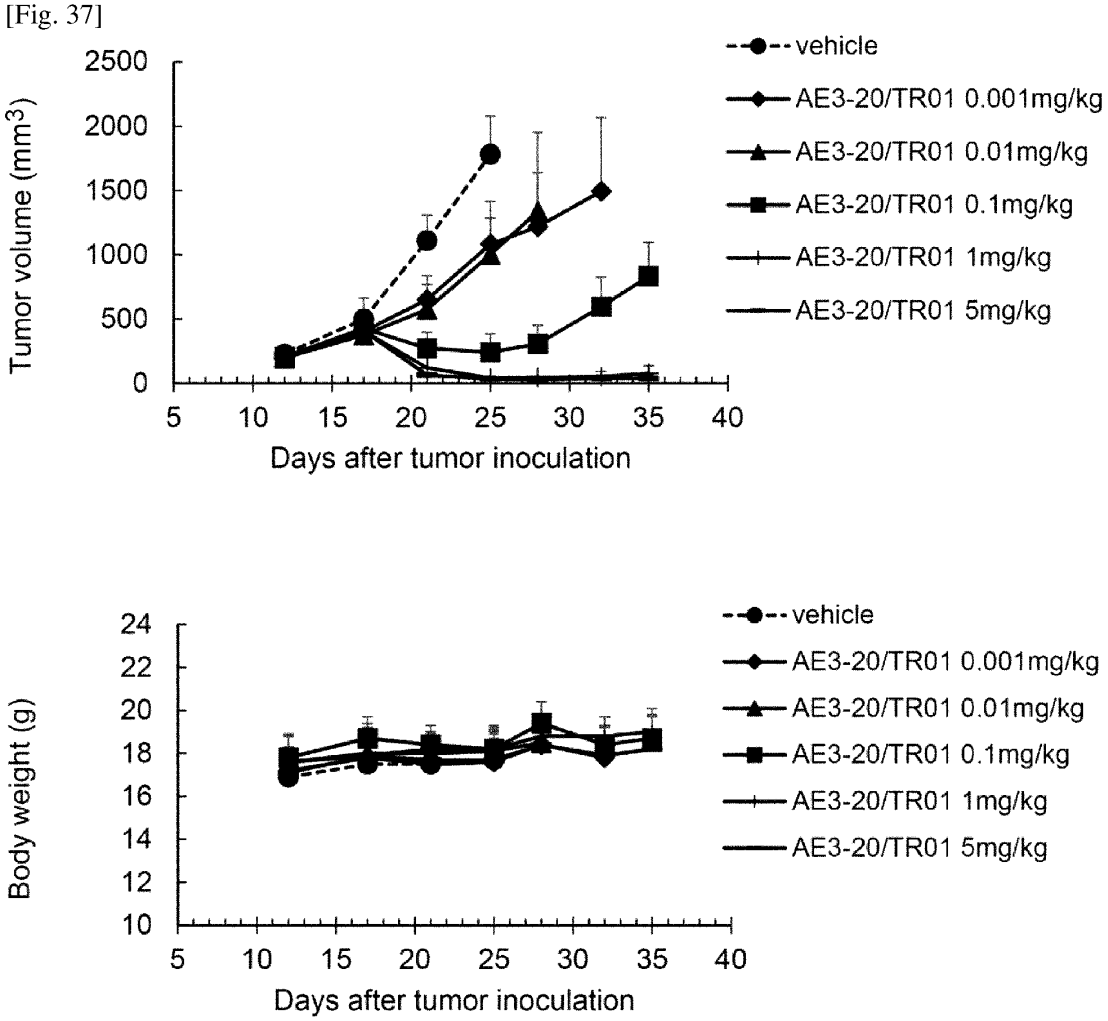
[Fig. 35-2]


AH05/TR01
6PHU3/TR01
hCLDN6/BaF3
hCLDN3/BaF3
hCLDN4/BaF3
hCLDN9/BaF3
CLDN6_AH05-P1
CLDN6_6PHU3-P1
CLDN3_AH05-P1
CLDN3_6PHU3-P1
CLDN4_AH05-P1
CLDN4_6PHU3-P1
CLDN9_AH05-P1
CLDN9_6PHU3-P1
Count
FITC-A
16752, 174
48021, 200
47969, 211
4153, 202
4093, 228
65, 206
3373, 198
2170, 240
KLH/TR01
CLDN6/CD3 bispecific antibodies

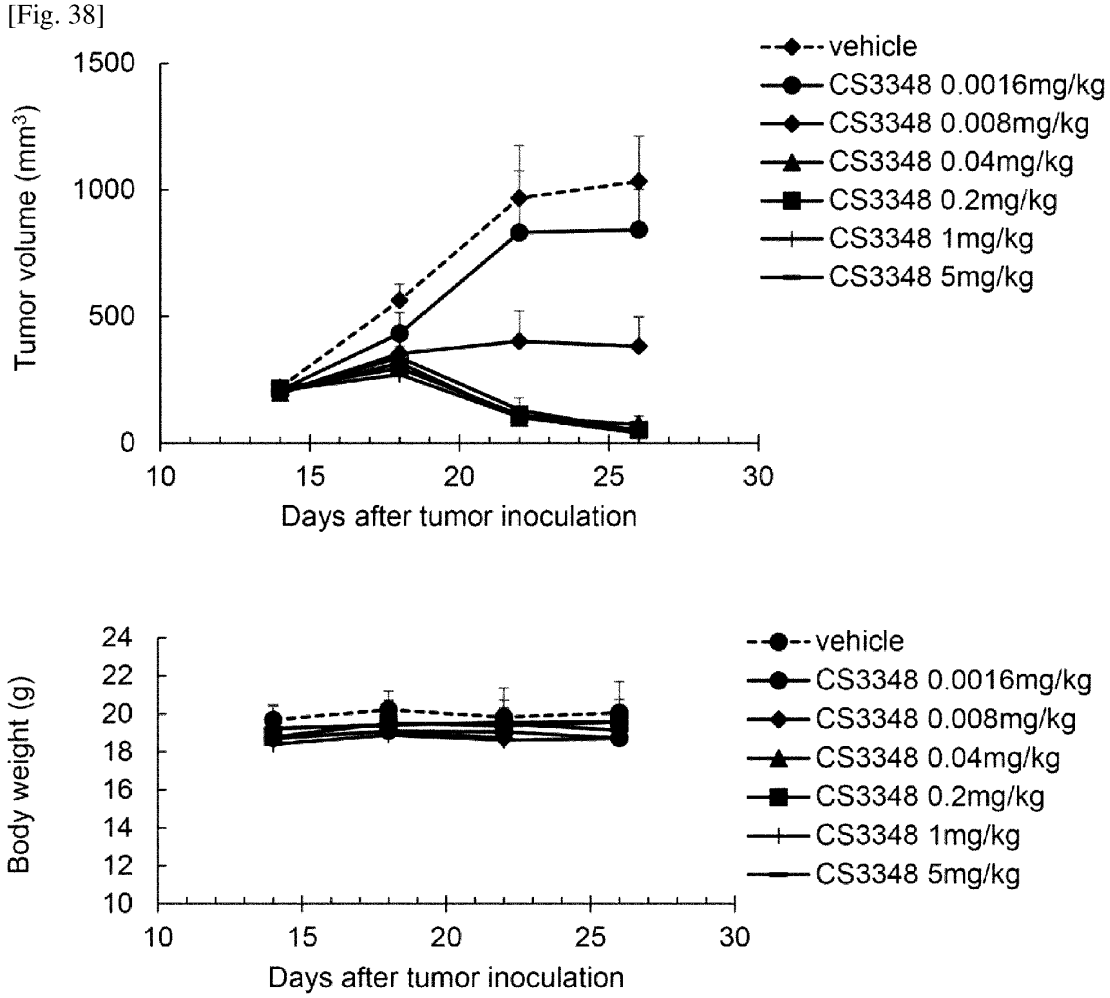
[Fig. 36]


initial
1 week
2 week
HMW (%)
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
CS2961
CS3346
CS3347
CS3348

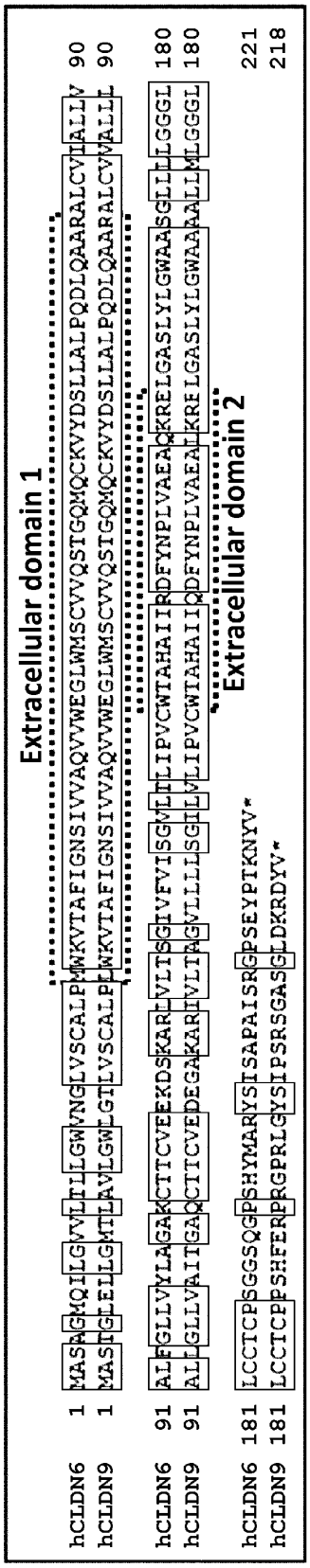
[Fig. 37]


Tumor volume (mm3)
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
40
Days after tumor inoculation
vehicle
AE3-20/TR01 0.001mg/kg
AE3-20/TR01 0.01mg/kg
AE3-20/TR01 0.1mg/kg
AE3-20/TR01 1mg/kg
AE3-20/TR01 5mg/kg
Body weight (g)
24
22
20
18
16
14
12
10
5
10
15
20
25
30
35
40
Days after tumor inoculation
vehicle
AE3-20/TR01 0.001mg/kg
AE3-20/TR01 0.01mg/kg
AE3-20/TR01 0.1mg/kg
AE3-20/TR01 1mg/kg
AE3-20/TR01 5mg/kg

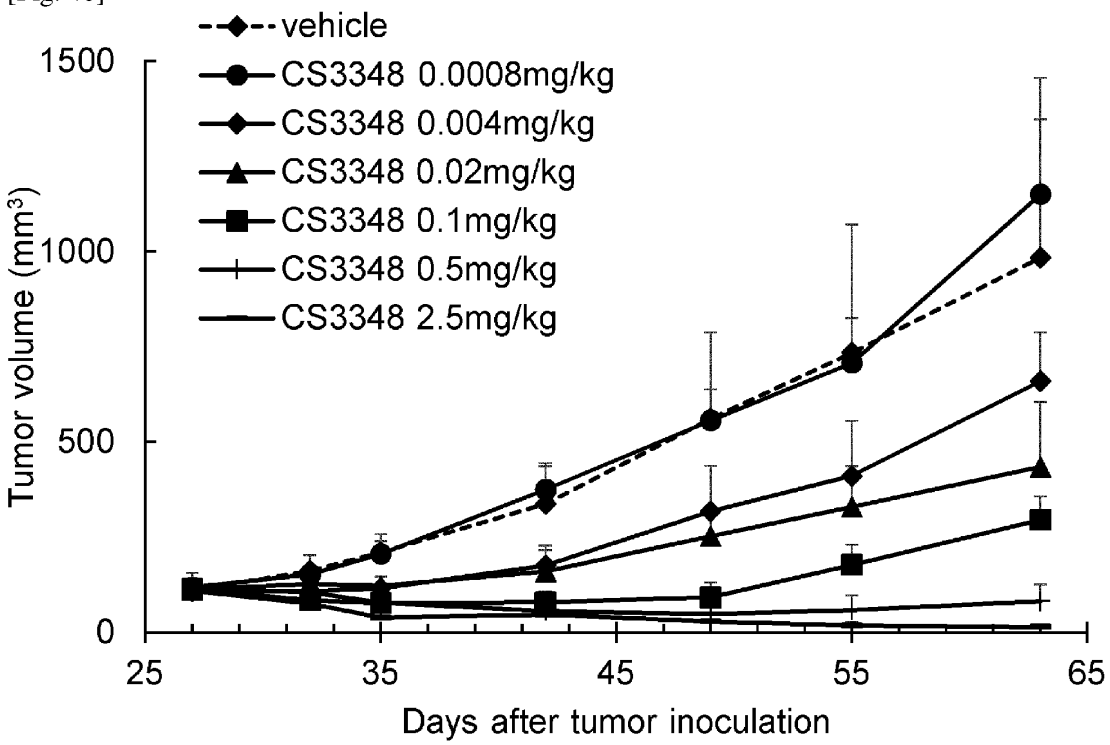
[Fig. 38]


Tumor volume (mm3)
1500
1000
500
0
10
15
20
25
30
Days after tumor inoculation
vehicle
CS3348 0.0016mg/kg
CS3348 0.008mg/kg
CS3348 0.04mg/kg
CS3348 0.2mg/kg
CS3348 1mg/kg
CS3348 5mg/kg
Body weight (g)
24
22
20
18
16
14
12
10
10
15
20
25
30
Days after tumor inoculation
vehicle
CS3348 0.0016mg/kg
CS3348 0.008mg/kg
CS3348 0.04mg/kg
CS3348 0.2mg/kg
CS3348 1mg/kg
CS3348 5mg/kg

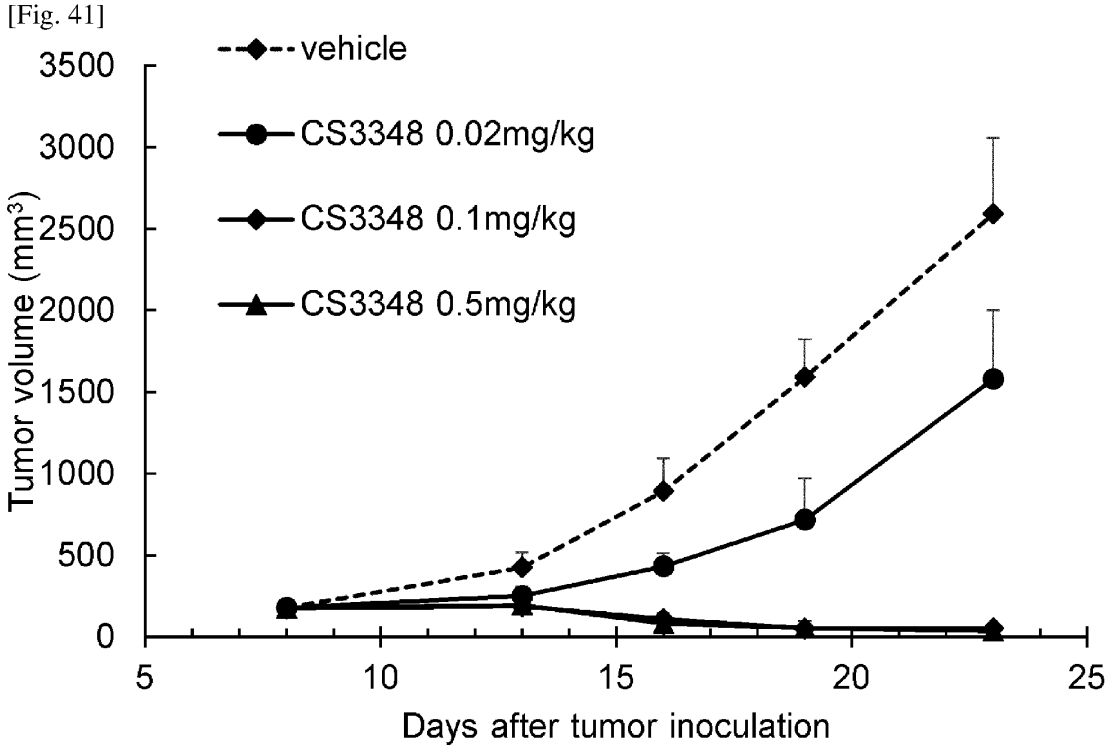
[Fig. 39]


Extracellular domain 1
Extracellular domain 2
hCLDN6 1 MASAGMQILGVVLTILGWVNGLVSCALPMWKVTAFIGNSIVVAQVVWEGLWMSCVVQSTGQMQCKVYDSLLALPQDLQAARALCVIALLV 90
hCLDN9 1 MASTGLELLGMTLAVLGWLGTLVSCALPLWKVTAFIGNSIVVAQVVWEGLWMSCVVQSTGQMQCKVYDSLLALPQDLQAARALCVMALLL 90
hCLDN6 91 ALFGLLVYLAGAKCTICVEEKDSKARLVLTSGIVFVISGMLLIPVCWTAHAIIRDFYNPLVAEAQKRELGASLYLGWAASGLLLLGGGL 180
hCLDN9 91 ALLGLLVAITGAQCTICVEDEGAKARLVLTAGVLLLLSGILVLIPVCWTAHAIIQDFYNPLVAEAQKRELGASLYLGWAAAALLMLGGGL 180
hCLDN6 181 LCCTCPSGGSQGPSHYMARYSTSAPAISRGPSEYPTKNYV* 221
hCLDN9 181 LCCTCPPSHFERPRGPRLGYSIPSRSGASGLDKRDYV* 218

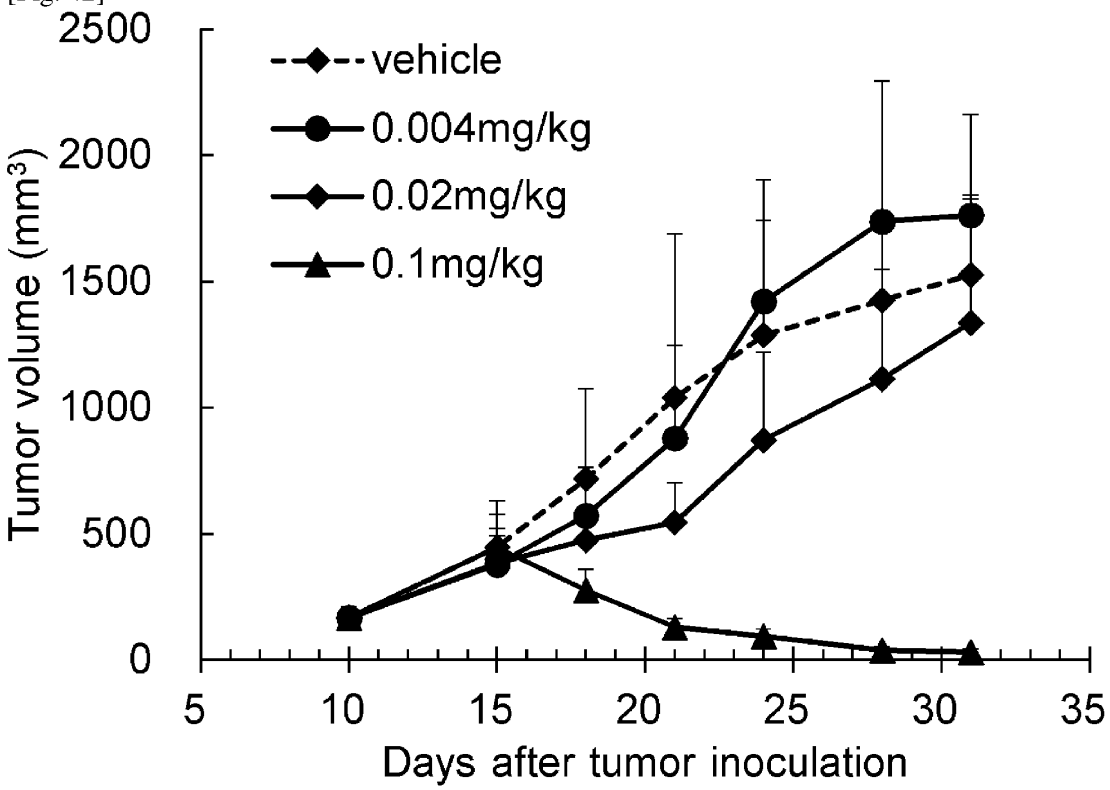
[Fig. 40]


vehicle
CS3348 0.0008mg/kg
CS3348 0.004mg/kg
CS3348 0.02mg/kg
CS3348 0.1mg/kg
CS3348 0.5mg/kg
CS3348 2.5mg/kg
Tumor volume (mm3)
1500
1000
500
0
25
35
45
55
65
Days after tumor inoculation

[Fig. 41]


vehicle
CS3348 0.02mg/kg
CS3348 0.1mg/kg
CS3348 0.5mg/kg
Tumor volume (mm3)
3500
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
Days after tumor inoculation

[Fig. 42]


2500
2000
1500
1000
500
0
Tumor volume (mm3)
vehicle
0.004mg/kg
0.02mg/kg
0.1mg/kg
5
10
15
20
25
30
35
Days after tumor inoculation