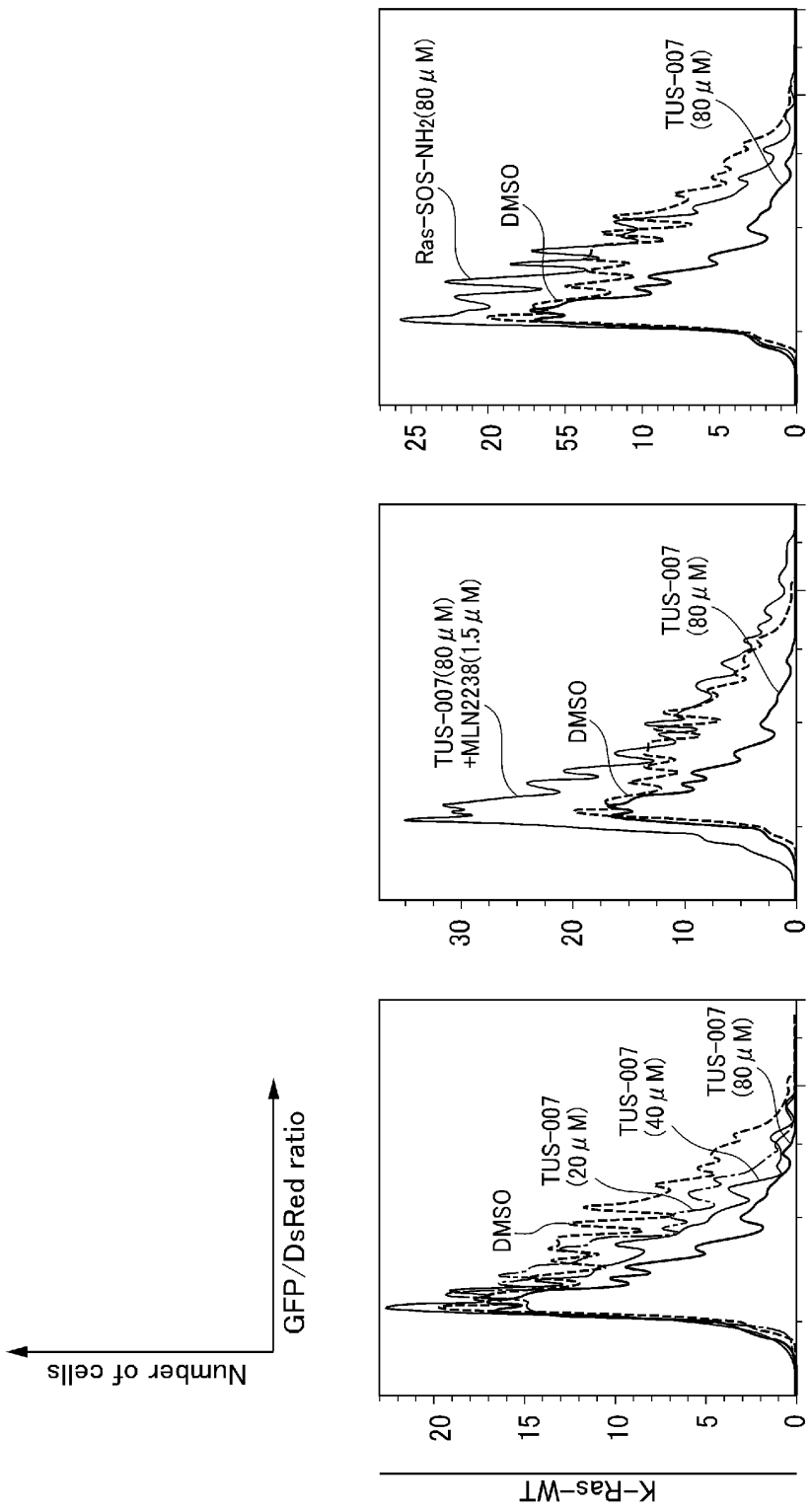
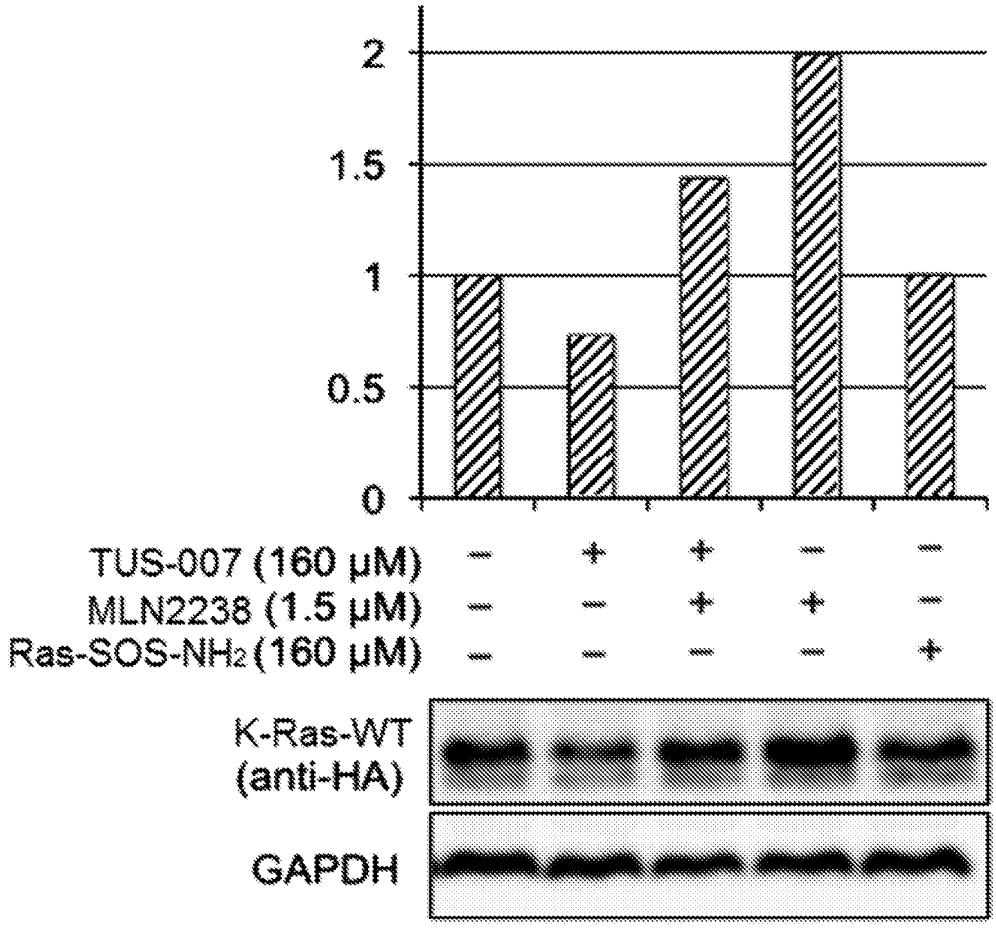
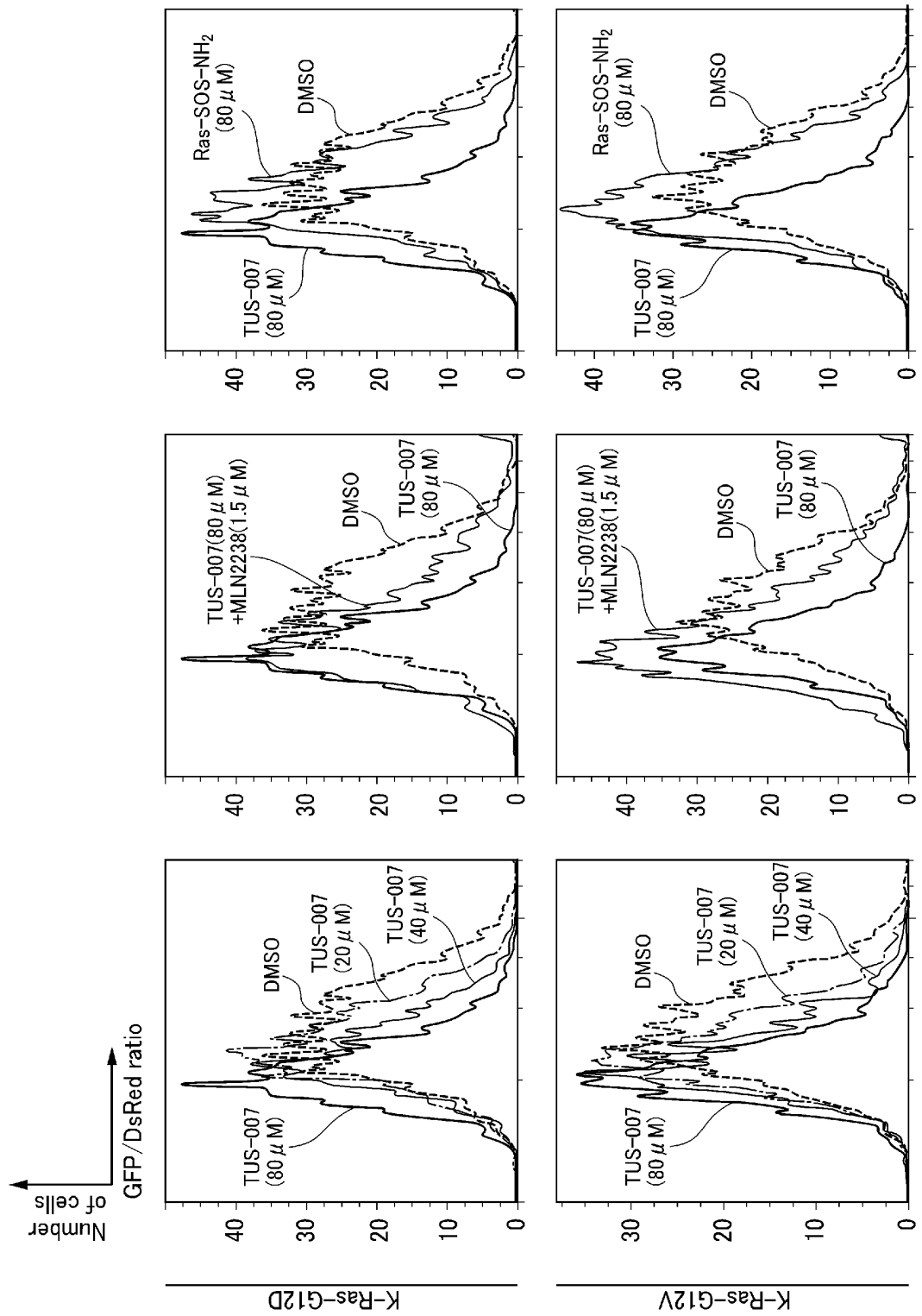
[図1]


K-Ras-WT
Number of cells
GFP/DsRed ratio
DMSO
TUS-007 (20 μM)
TUS-007 (40 μM)
TUS-007 (80 μM)
TUS-007(80 μM) +MLN2238(1.5 μM)
Ras-SOS-NH2(80 μM)

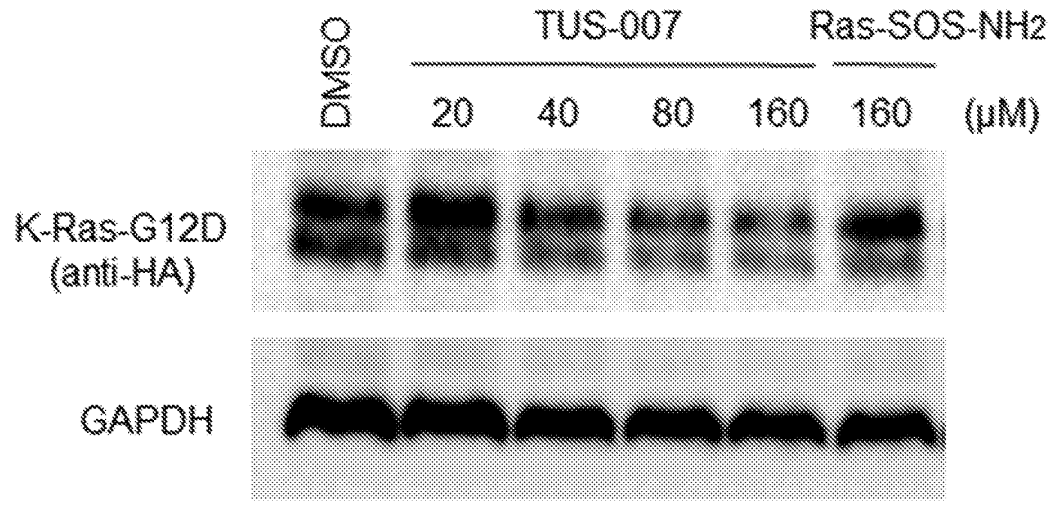
[図2]


2
1.5
1
0.5
0
TUS-007 (160 μM) − + + − −
MLN2238 (1.5 μM) − − + + −
Ras-SOS-NH2 (160 μM) − − − − +
K-Ras-WT
(anti-HA)
GAPDH

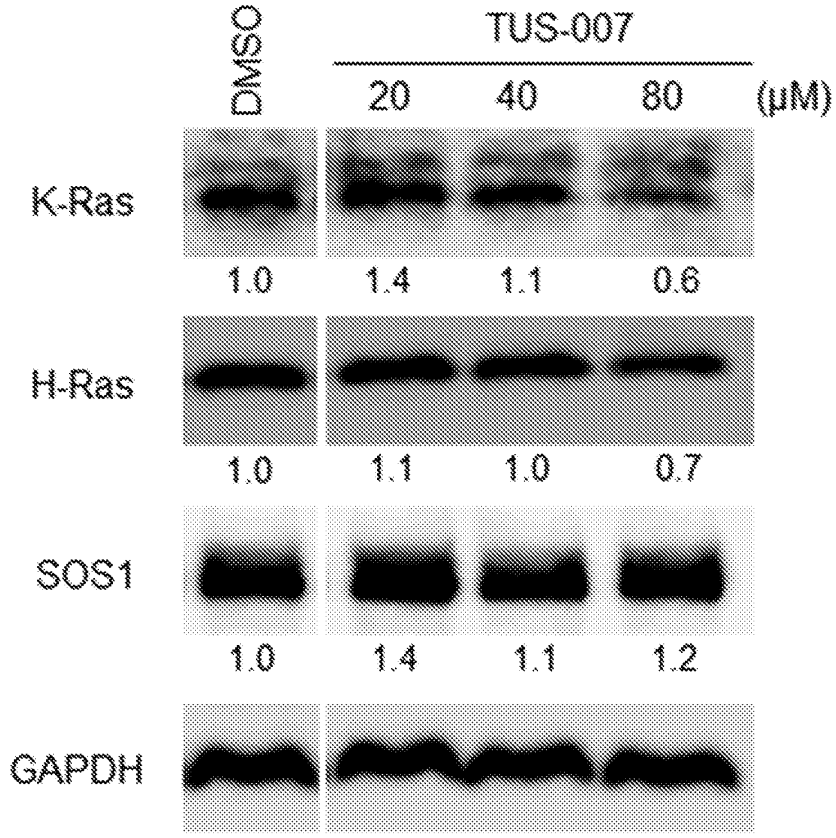
[図3]


Number of cells
GFP/DsRed ratio
K-Ras-G12D
K-Ras-G12V
TUS-007 (80 μM)
DMSO
TUS-007 (20 μM)
TUS-007 (40 μM)
TUS-007(80 μM) +MLN2238(1.5 μM)
Ras-SOS-NH2 (80 μM)
0
10
20
30
40

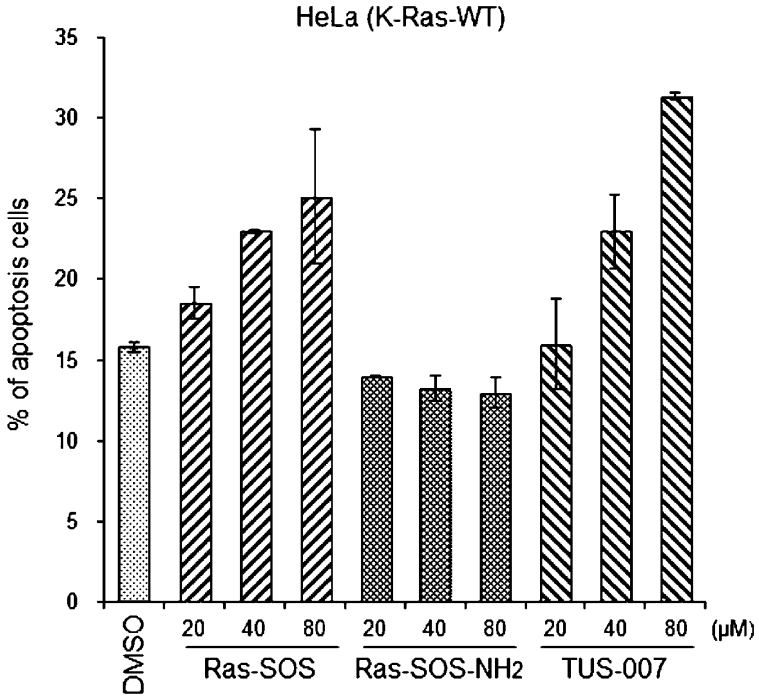
[図4]


DMSO
TUS-007
Ras-SOS-NH2
20
40
80
160
160
(μM)
K-Ras-G12D
(anti-HA)
GAPDH

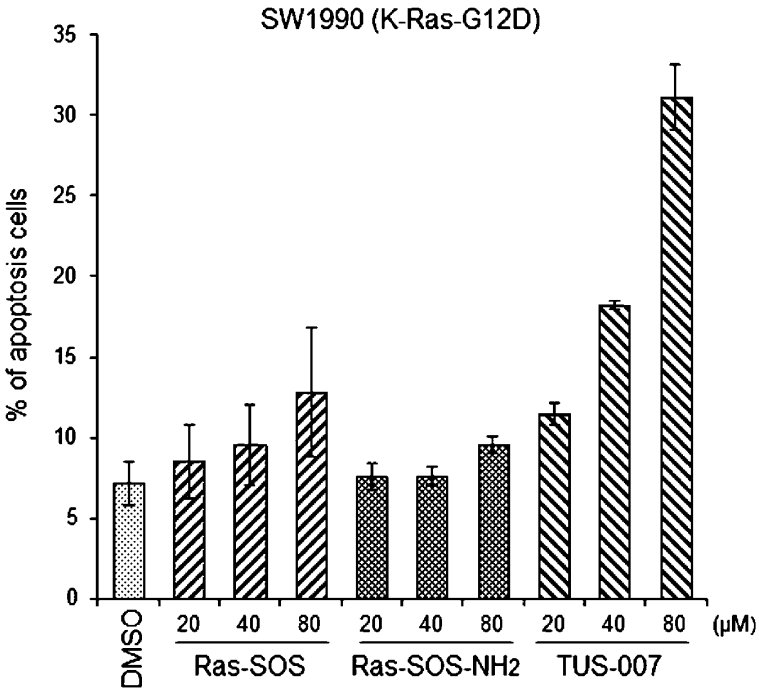
[図5]


DMSO
TUS-007
20
40
80
(μM)
K-Ras
1.0
1.4
1.1
0.6
H-Ras
1.0
1.1
1.0
0.7
SOS1
1.0
1.4
1.1
1.2
GAPDH

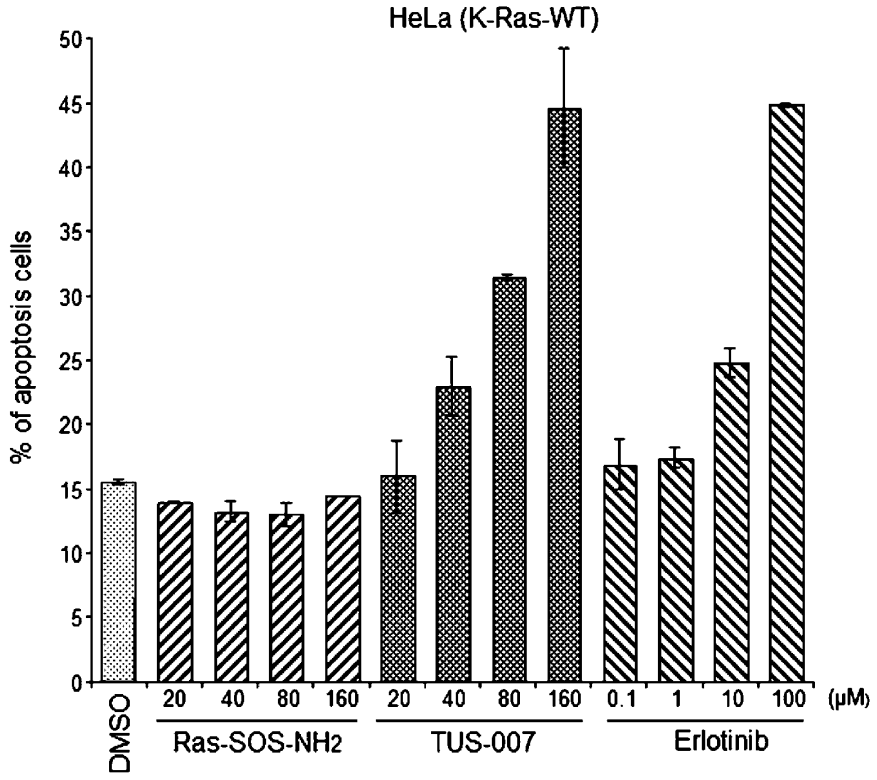
[図6A]


HeLa (K-Ras-WT)
% of apoptosis cells
35
30
25
20
15
10
5
0
DMSO
20
40
80
20
40
80
20
40
80
(μM)
Ras-SOS
Ras-SOS-NH2
TUS-007

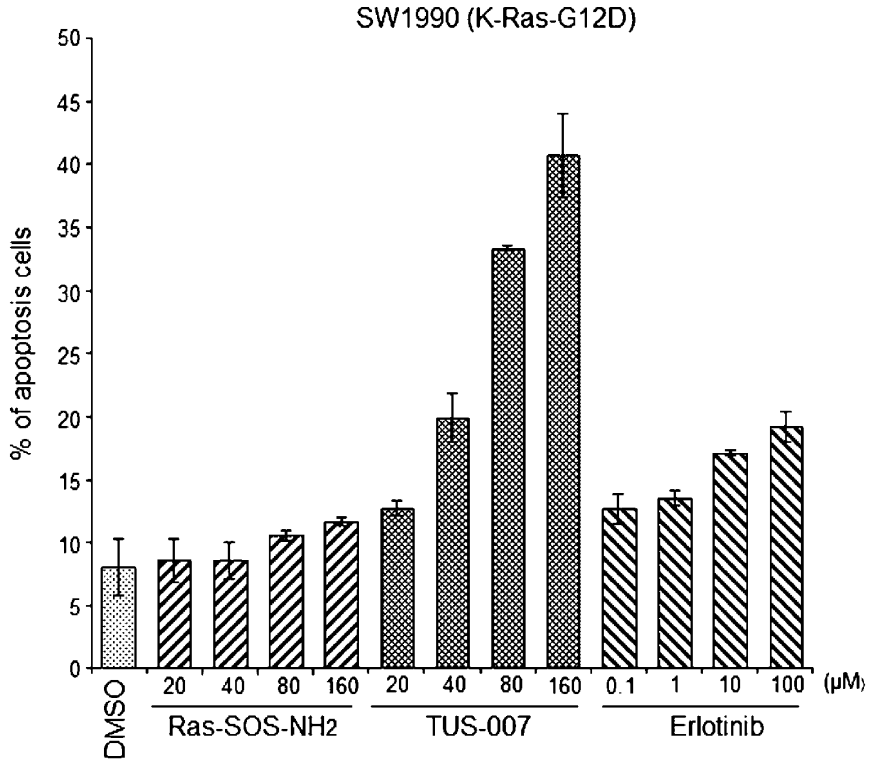
[図6B]


SW1990 (K-Ras-G12D)
% of apoptosis cells
35
30
25
20
15
10
5
0
DMSO
20
40
80
20
40
80
20
40
80
(μM)
Ras-SOS
Ras-SOS-NH2
TUS-007

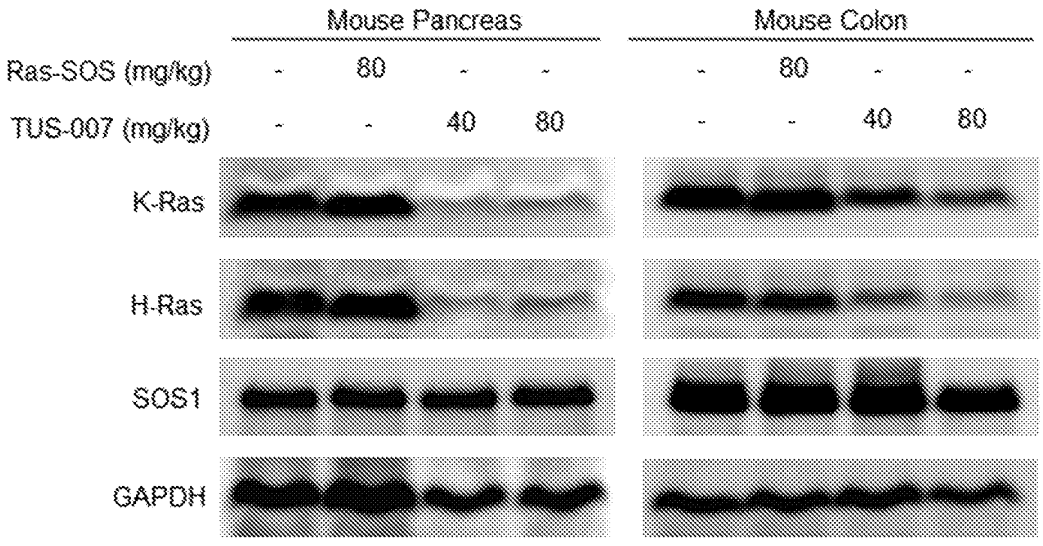
[図7A]


HeLa (K-Ras-WT)
% of apoptosis cells
50
45
40
35
30
25
20
15
10
5
0
DMSO
20
40
80
160
20
40
80
160
0.1
1
10
100
(μM)
Ras-SOS-NH2
TUS-007
Erlotinib

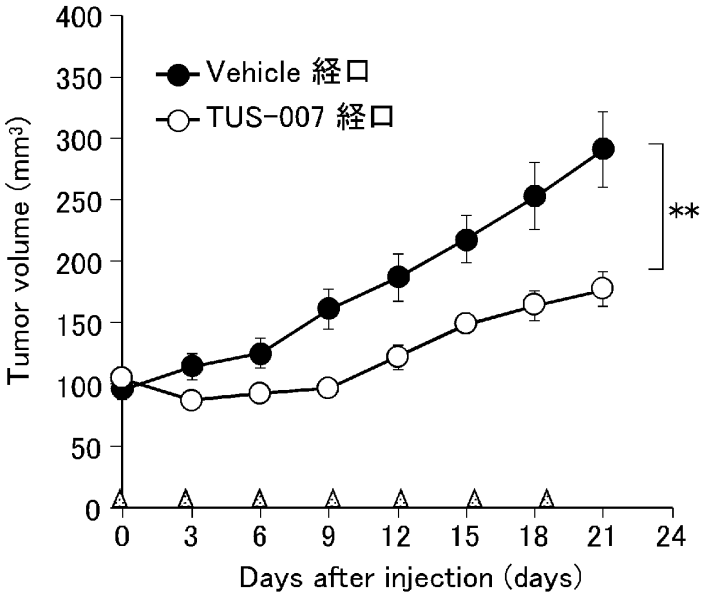
[図7B]


SW1990 (K-Ras-G12D)
% of apoptosis cells
50
45
40
35
30
25
20
15
10
5
0
DMSO
20
40
80
160
20
40
80
160
0.1
1
10
100
(μM)
Ras-SOS-NH2
TUS-007
Erlotinib

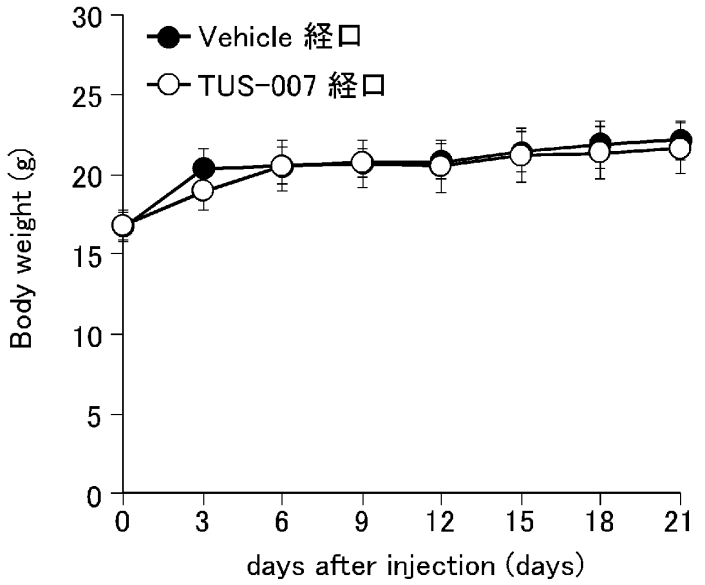
[図8]


Mouse Pancreas
Mouse Colon
Ras-SOS (mg/kg)
TUS-007 (mg/kg)
K-Ras
H-Ras
SOS1
GAPDH

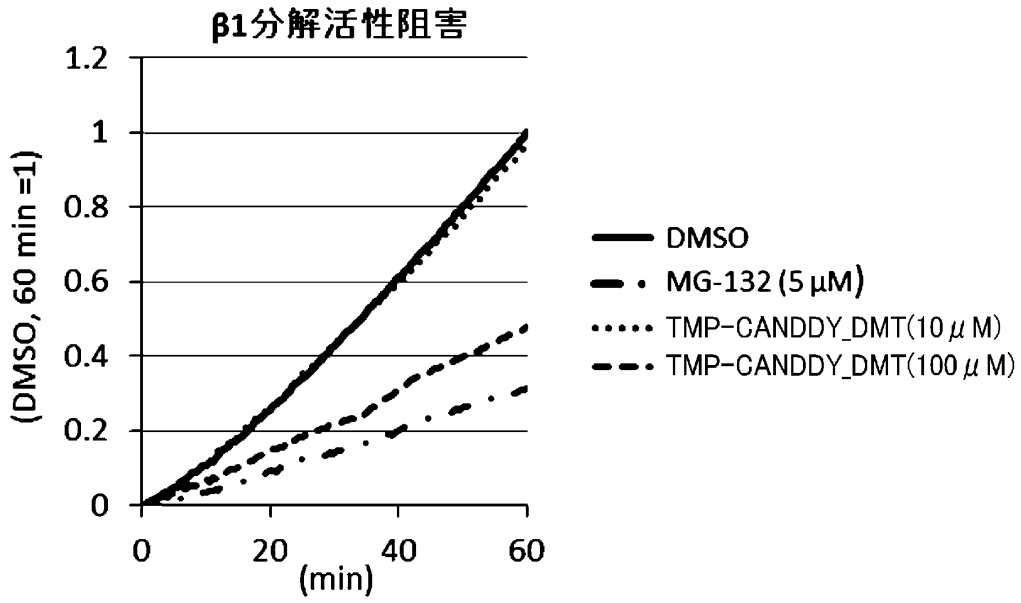
[図9A]


Vehicle 経口
TUS-007 経口
Tumor volume (mm3)
400
350
300
250
200
150
100
50
0
0
3
6
9
12
15
18
21
24
Days after injection (days)
**

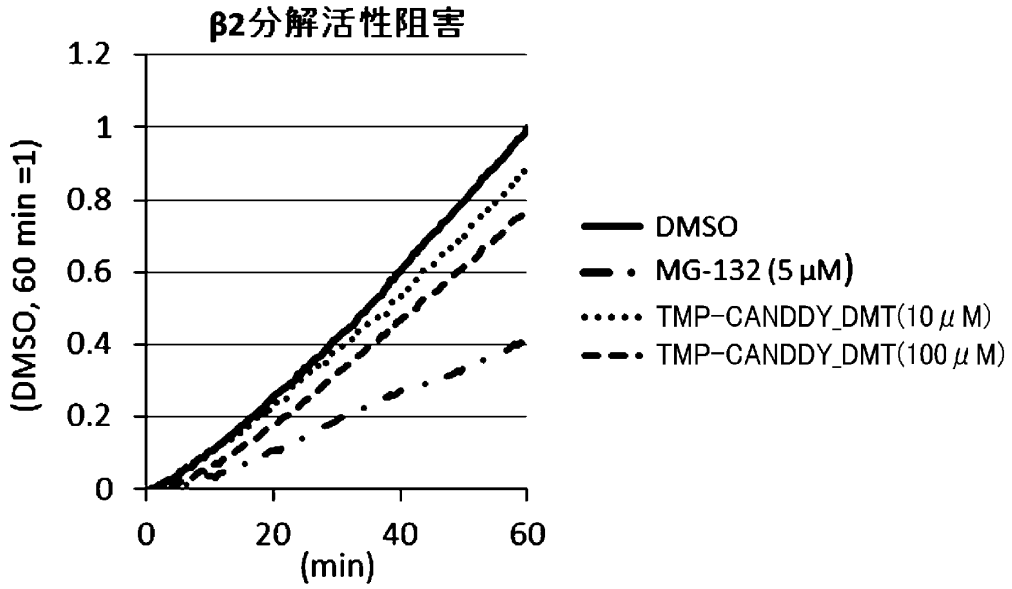
[図9B]


Vehicle 経口
TUS-007 経口
Body weight (g)
30
25
20
15
10
5
0
0
3
6
9
12
15
18
21
days after injection (days)

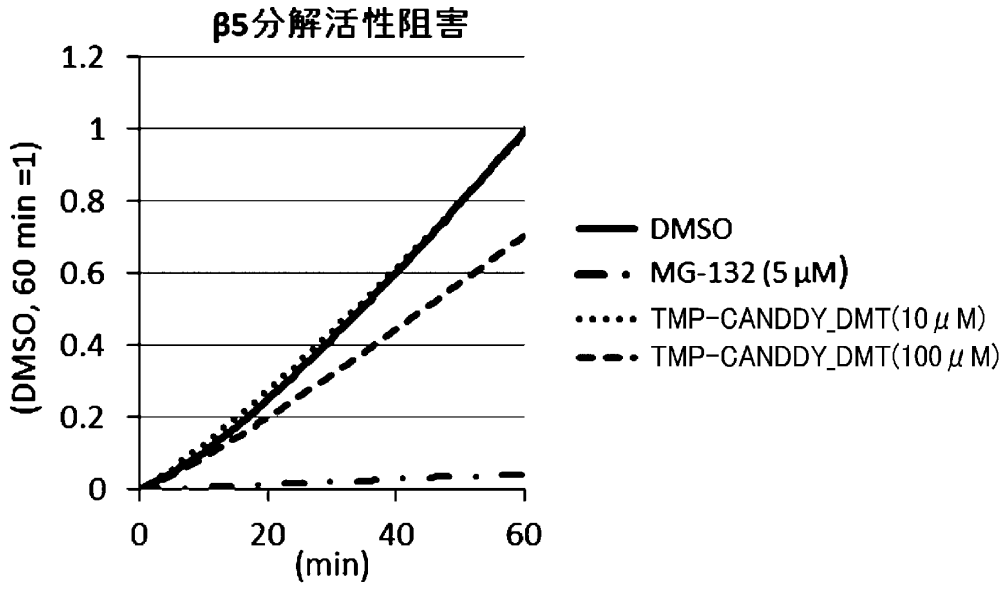
[図10A]


β1分解活性阻害
(DMSO, 60 min =1)
1.2
1
0.8
0.6
0.4
0.2
0
0
20
40
60
(min)
DMSO
MG-132 (5 μM)
TMP-CANDDY_DMT(10 μ M)
TMP-CANDDY_DMT(100 μ M)

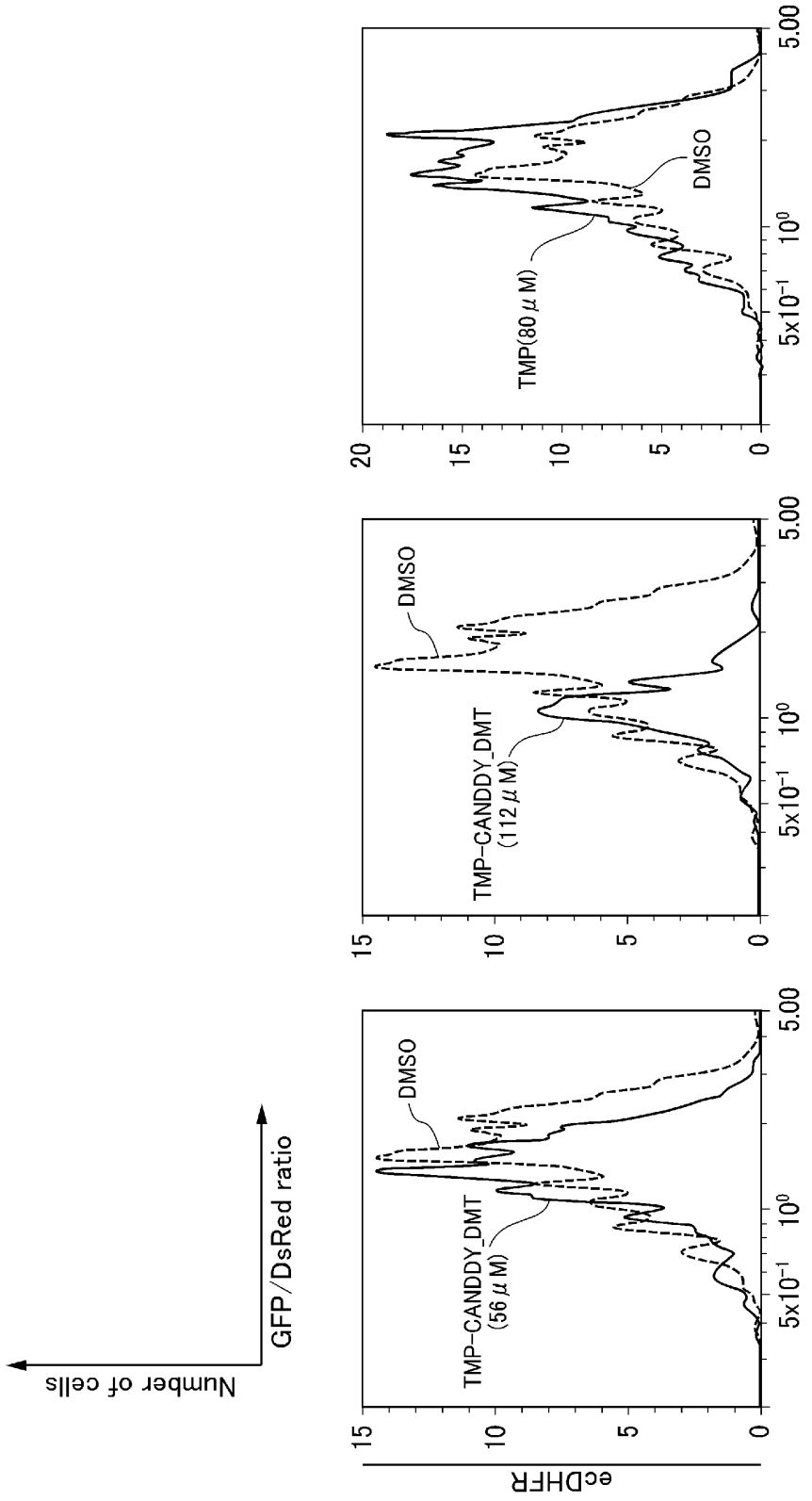
[図10B]


β2分解活性阻害
(DMSO, 60 min =1)
1.2
1
0.8
0.6
0.4
0.2
0
0
20
40
60
(min)
DMSO
MG-132 (5 μM)
TMP-CANDDY_DMT(10 μ M)
TMP-CANDDY_DMT(100 μ M)

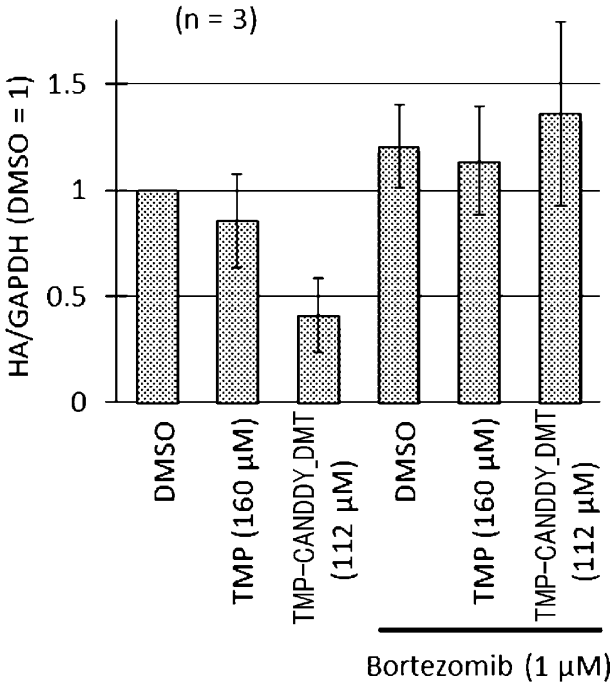
[図10C]


β5分解活性阻害
1.2
1
0.8
0.6
0.4
0.2
0
(DMSO, 60 min =1)
0
20
40
60
(min)
DMSO
MG-132 (5 μM)
TMP-CANDDY_DMT(10 μM)
TMP-CANDDY_DMT(100 μM)

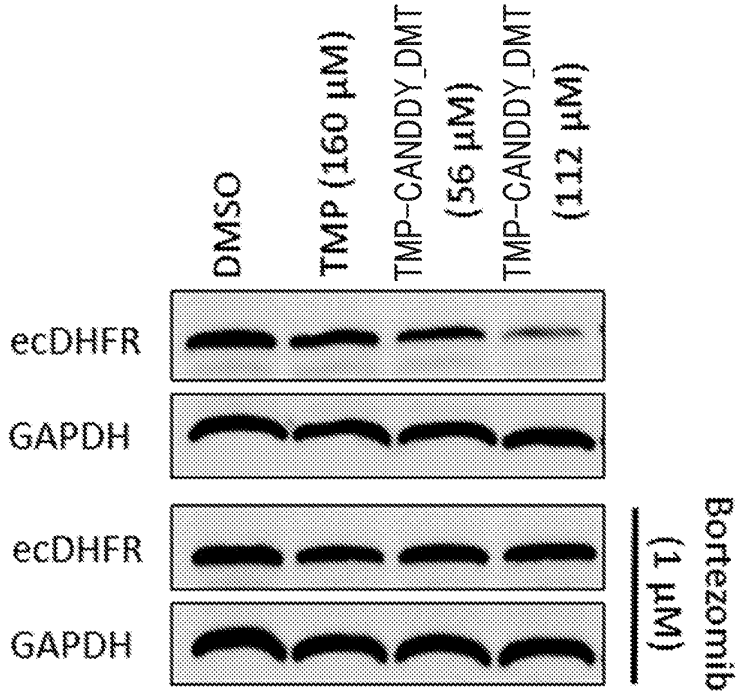
[図11]


ecDHFR
GFP/DsRed ratio
Number of cells
TMP(80 μ M)
DMSO
TMP-CANDDY_DMT
(112 μ M)
DMSO
TMP-CANDDY_DMT
(56 μ M)
DMSO
5x10⁻¹
10⁰
5.00
0
5
10
15
20

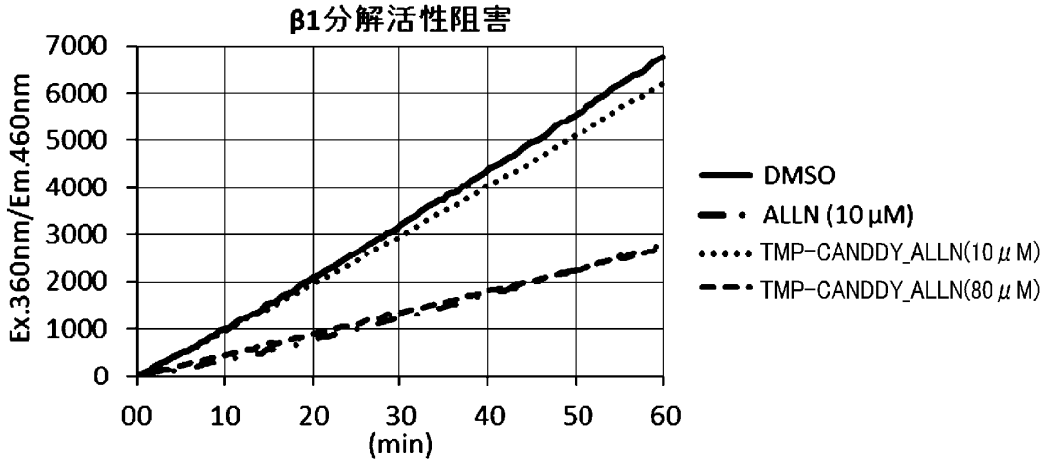
[図12A]


(n = 3)
HA/GAPDH (DMSO = 1)
1.5
1
0.5
0
DMSO
TMP (160 μM)
TMP-CANDDY_DMT (112 μM)
DMSO
TMP (160 μM)
TMP-CANDDY_DMT (112 μM)
Bortezomib (1 μM)

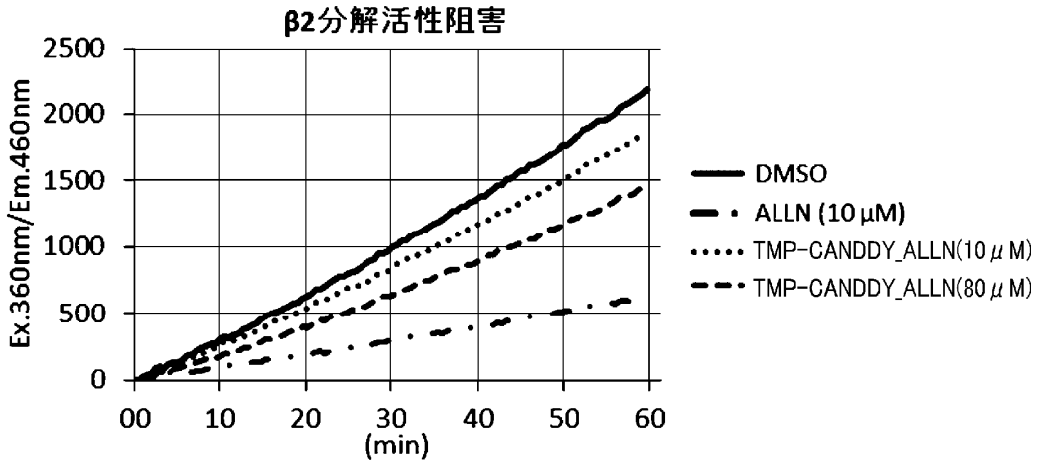
[図12B]


DMSO
TMP (160 μM)
TMP-CANDDY_DMT (56 μM)
TMP-CANDDY_DMT (112 μM)
ecDHFR
GAPDH
ecDHFR
GAPDH
Bortezomib (1 μM)

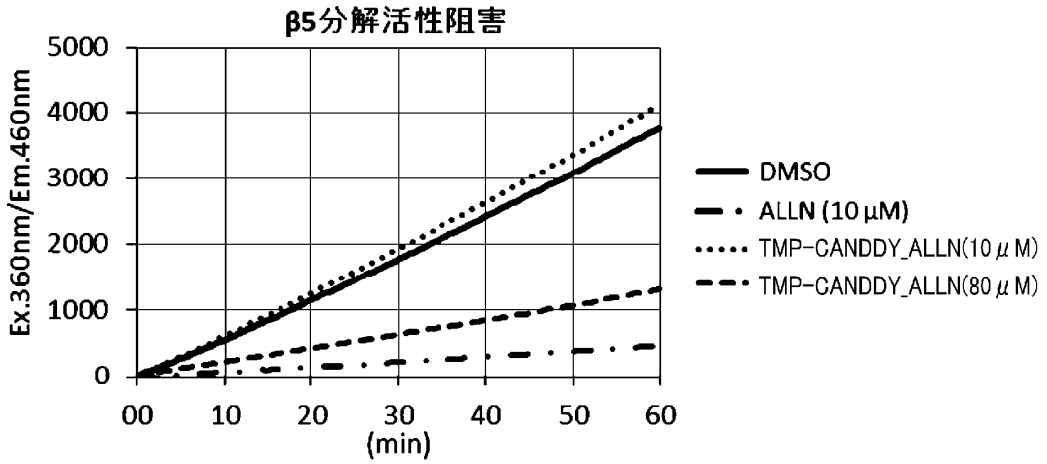
[図13A]



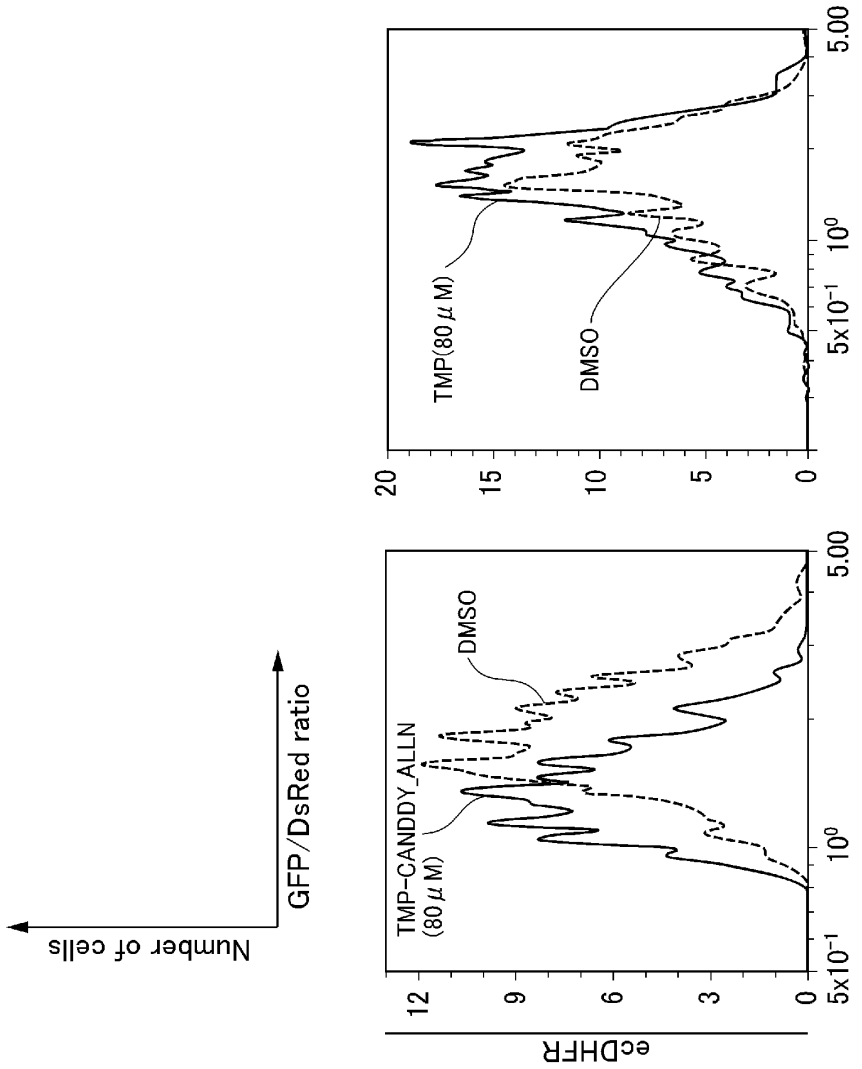
[図13B]



[図13C]



[図14]


ecDHFR
TMP-CANDDY_ALLN (80μM)
DMSO
TMP(80μM)
DMSO
Number of cells
GFP/DsRed ratio
0
3
6
9
12
0
5
10
15
20
5x10⁻¹
10⁰
5.00