Figure 1-1

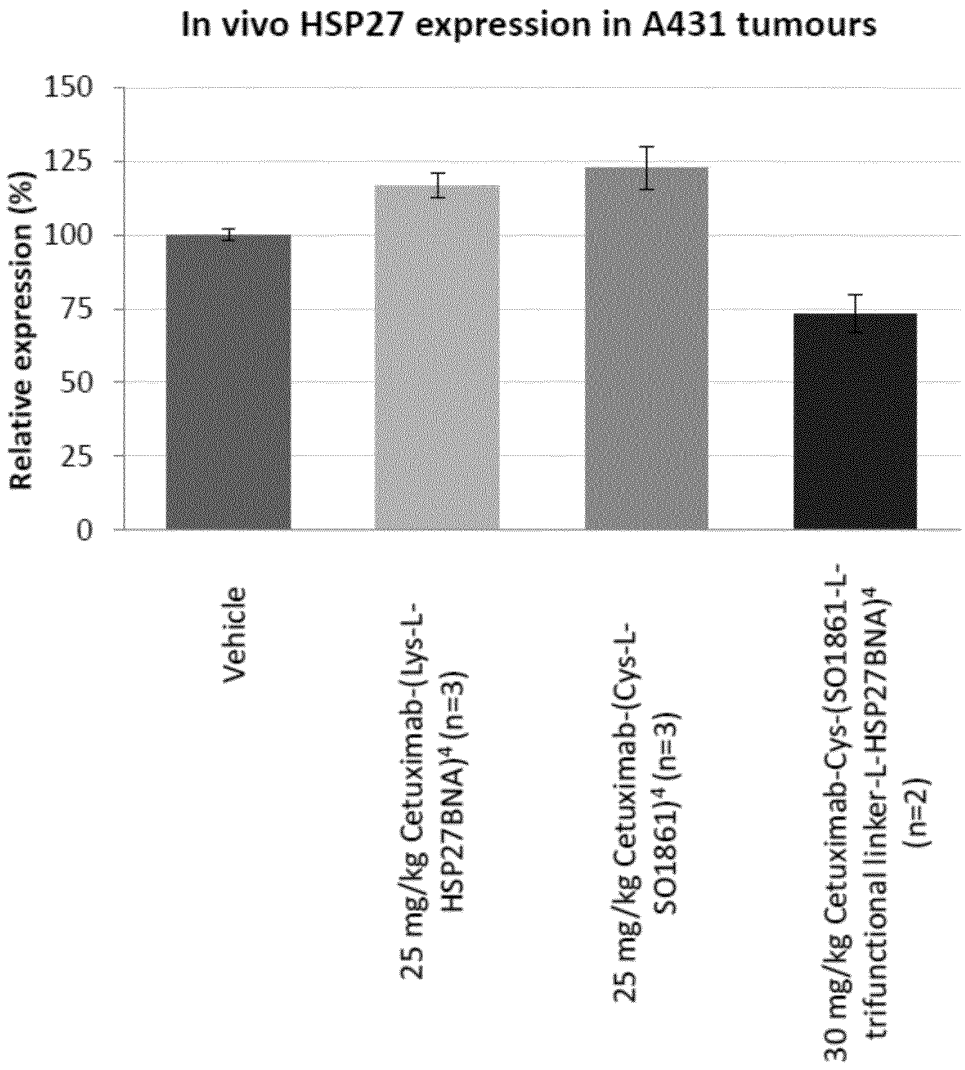

In vivo HSP27 expression in A431 tumours
Relative expression (%)
150
125
100
75
50
25
0
Vehicle
25 mg/kg Cetuximab-(Lys-L-HSP27BNA)4 (n=3)
25 mg/kg Cetuximab-(Cys-L-SO1861)4 (n=3)
30 mg/kg Cetuximab-Cys-(SO1861-L-trifunctional linker-L-HSP27BNA)4 (n=2)

Figure 2-1

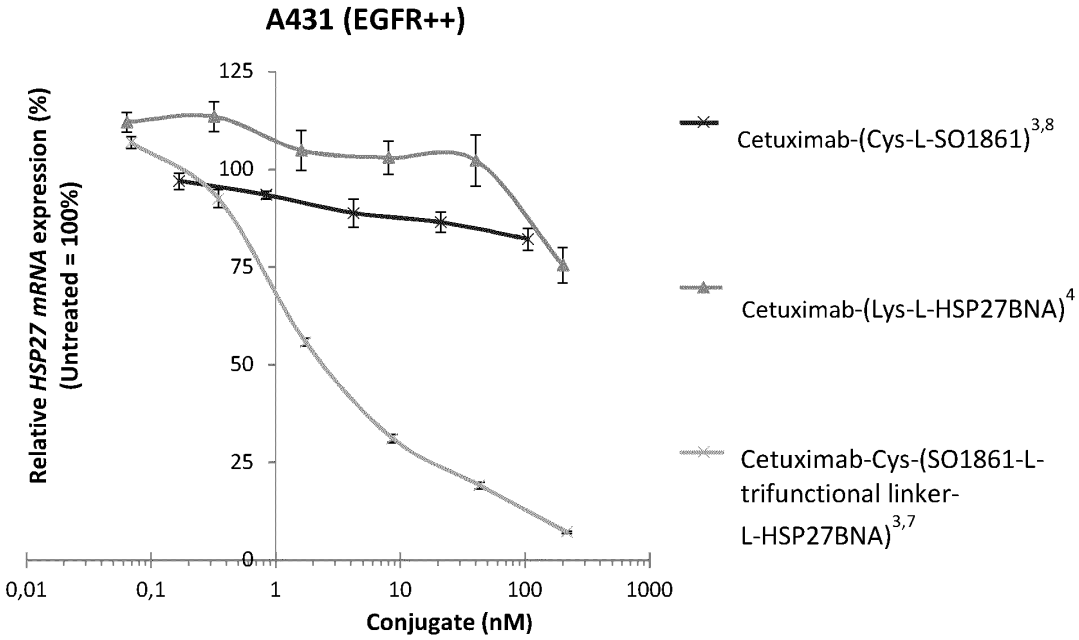


Figure 3-1

A

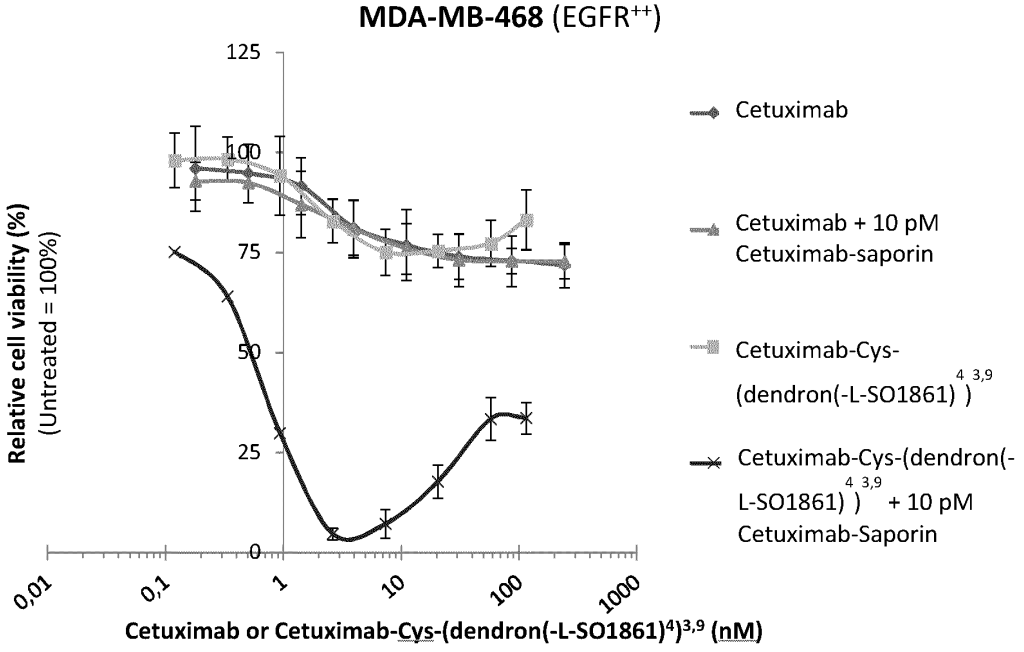
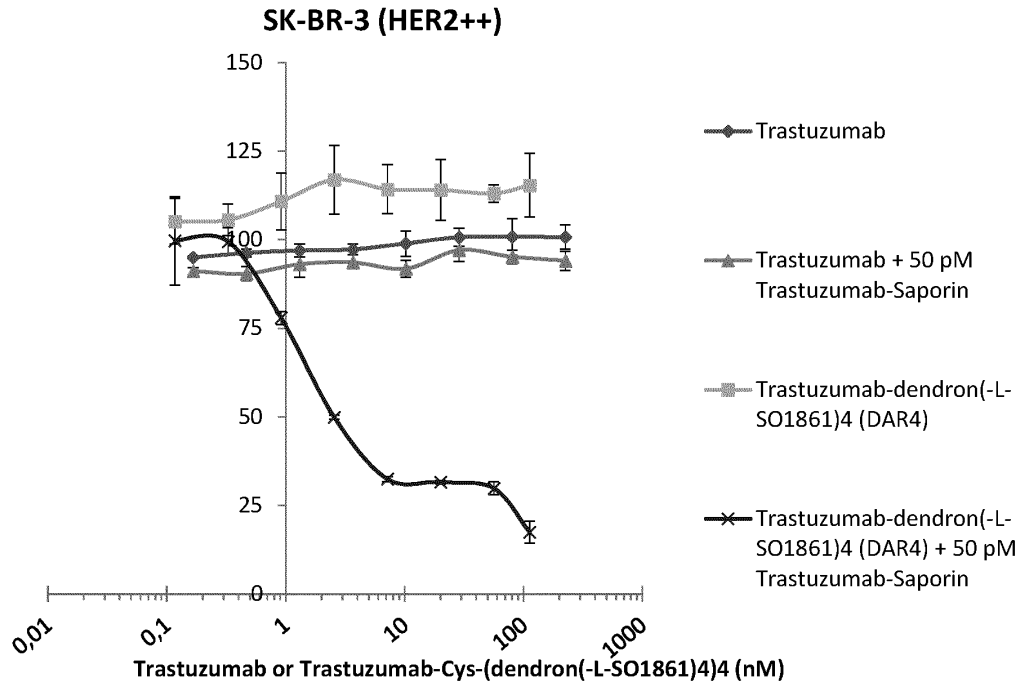


Figure 3-1

B


SK-BR-3 (HER2++)
150
125
100
75
50
25
0
0,01
0,1
1
10
100
1000
Trastuzumab or Trastuzumab-Cys-(dendron(-L-SO1861)4)4 (nM)
Trastuzumab
Trastuzumab + 50 pM Trastuzumab-Saporin
Trastuzumab-dendron(-L-SO1861)4 (DAR4)
Trastuzumab-dendron(-L-SO1861)4 (DAR4) + 50 pM Trastuzumab-Saporin

C

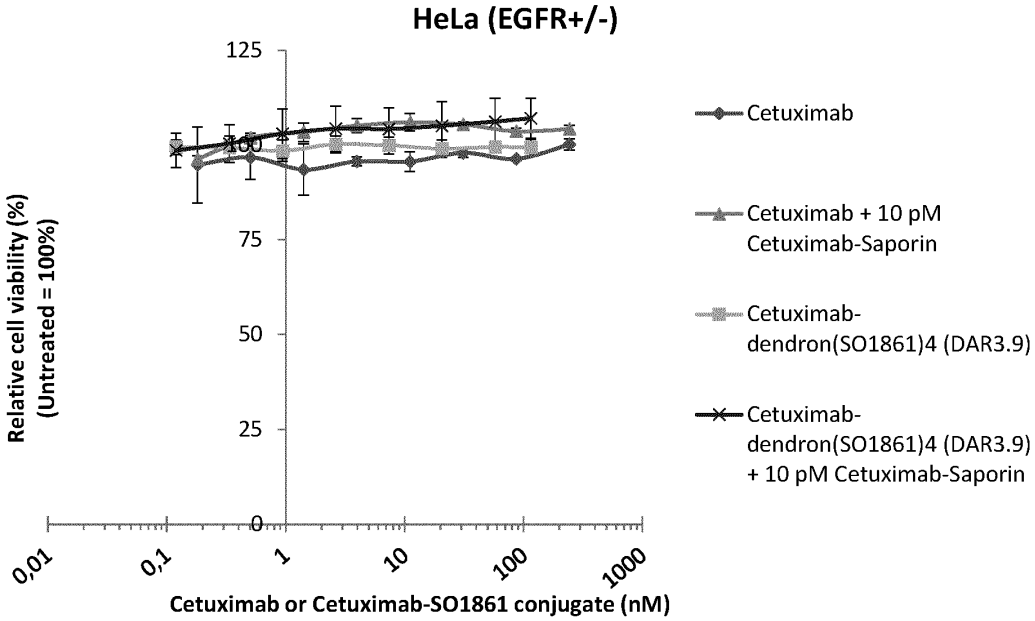

HeLa (EGFR+/-)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,01
0,1
1
10
100
1000
Cetuximab or Cetuximab-SO1861 conjugate (nM)
Cetuximab
Cetuximab + 10 pM Cetuximab-Saporin
Cetuximab-dendron(SO1861)4 (DAR3.9)
Cetuximab-dendron(SO1861)4 (DAR3.9) + 10 pM Cetuximab-Saporin

Figure 3-1
D

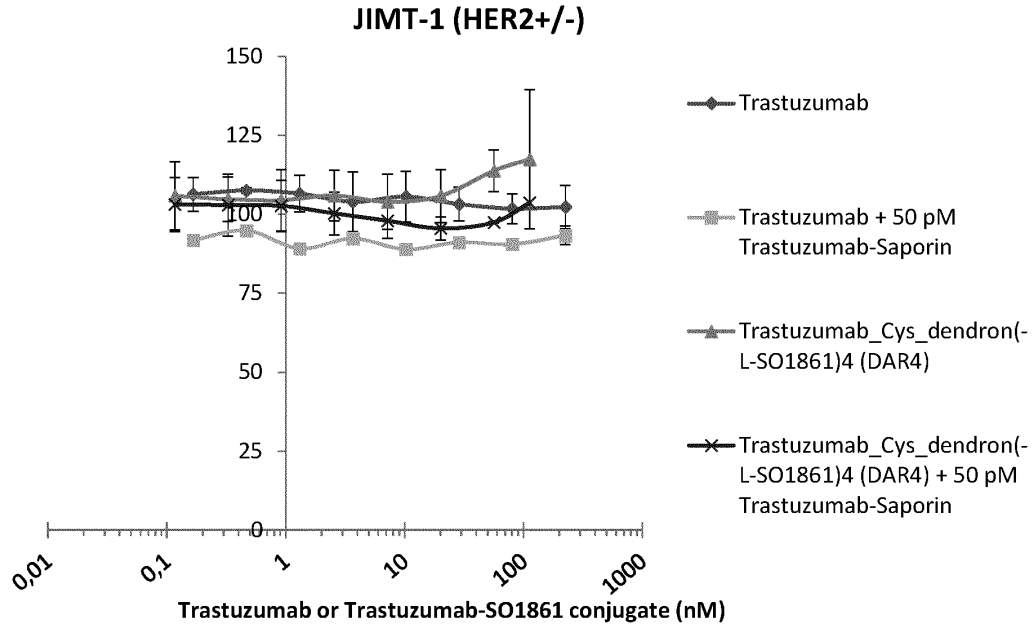


Figure 4-1
A

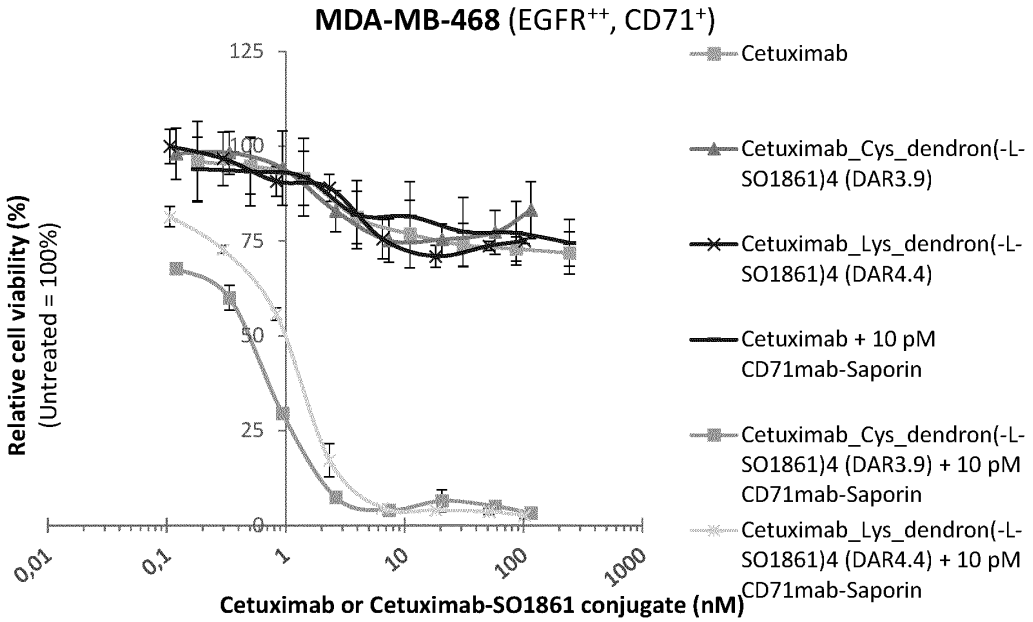
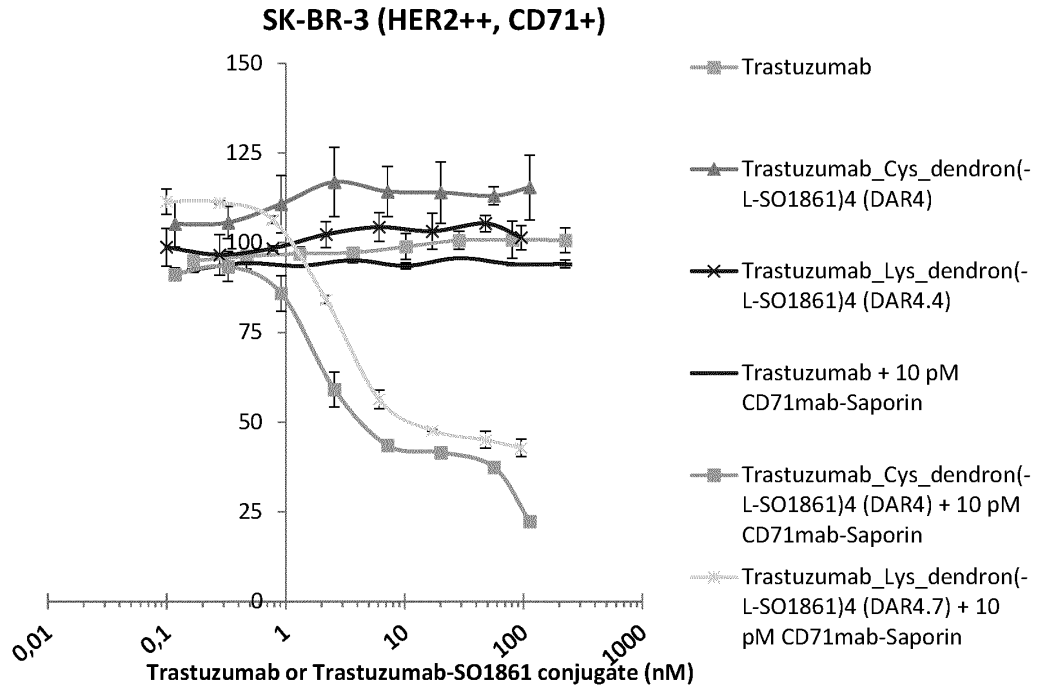


Figure 4-1

B


SK-BR-3 (HER2++, CD71+)
150
125
100
75
50
25
0
0,01
0,1
1
10
100
1000
Trastuzumab or Trastuzumab-SO1861 conjugate (nM)
Trastuzumab
Trastuzumab_Cys_dendron(-L-SO1861)4 (DAR4)
Trastuzumab_Lys_dendron(-L-SO1861)4 (DAR4.4)
Trastuzumab + 10 pM CD71mab-Saporin
Trastuzumab_Cys_dendron(-L-SO1861)4 (DAR4) + 10 pM CD71mab-Saporin
Trastuzumab_Lys_dendron(-L-SO1861)4 (DAR4.7) + 10 pM CD71mab-Saporin

C

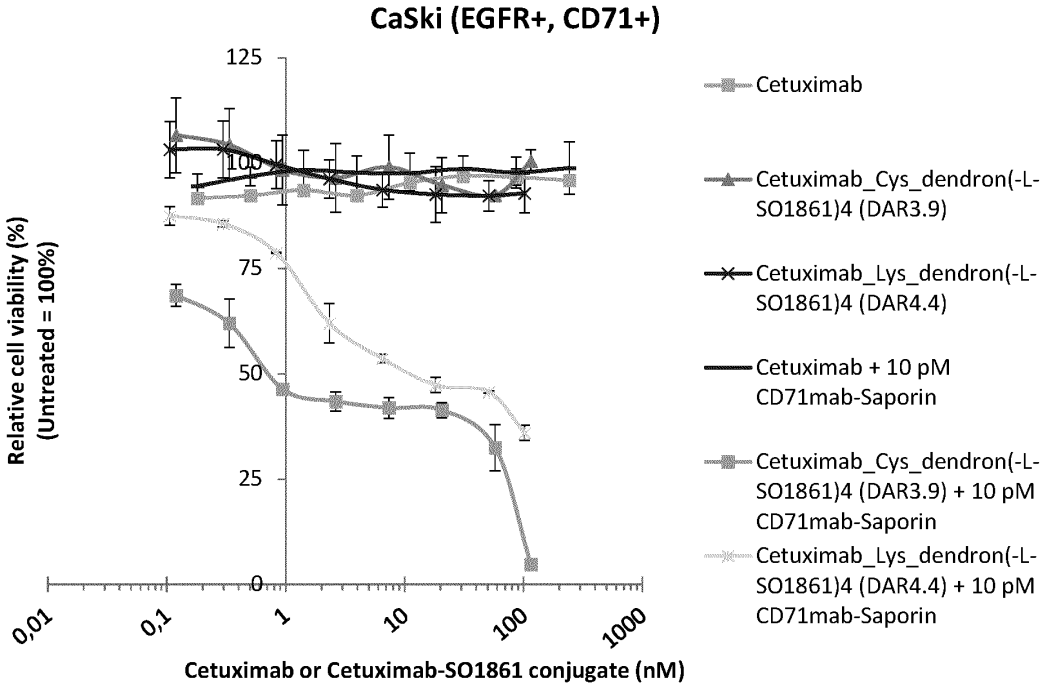

CaSki (EGFR+, CD71+)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,01
0,1
1
10
100
1000
Cetuximab or Cetuximab-SO1861 conjugate (nM)
Cetuximab
Cetuximab_Cys_dendron(-L-SO1861)4 (DAR3.9)
Cetuximab_Lys_dendron(-L-SO1861)4 (DAR4.4)
Cetuximab + 10 pM CD71mab-Saporin
Cetuximab_Cys_dendron(-L-SO1861)4 (DAR3.9) + 10 pM CD71mab-Saporin
Cetuximab_Lys_dendron(-L-SO1861)4 (DAR4.4) + 10 pM CD71mab-Saporin

Figure 4-1
D

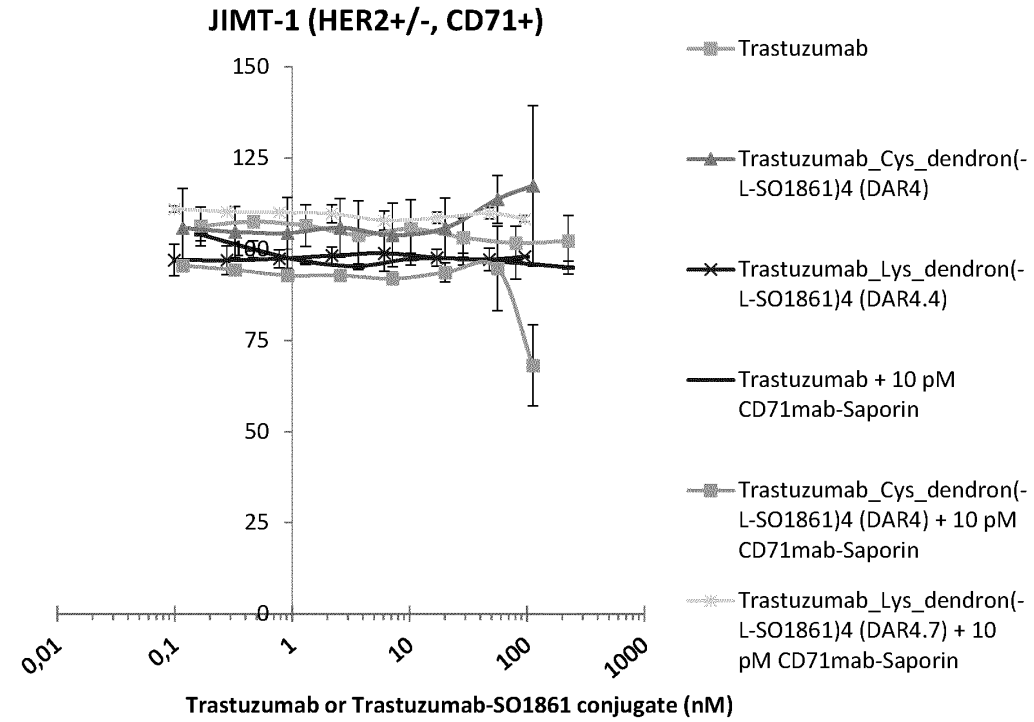


Figure 5-1

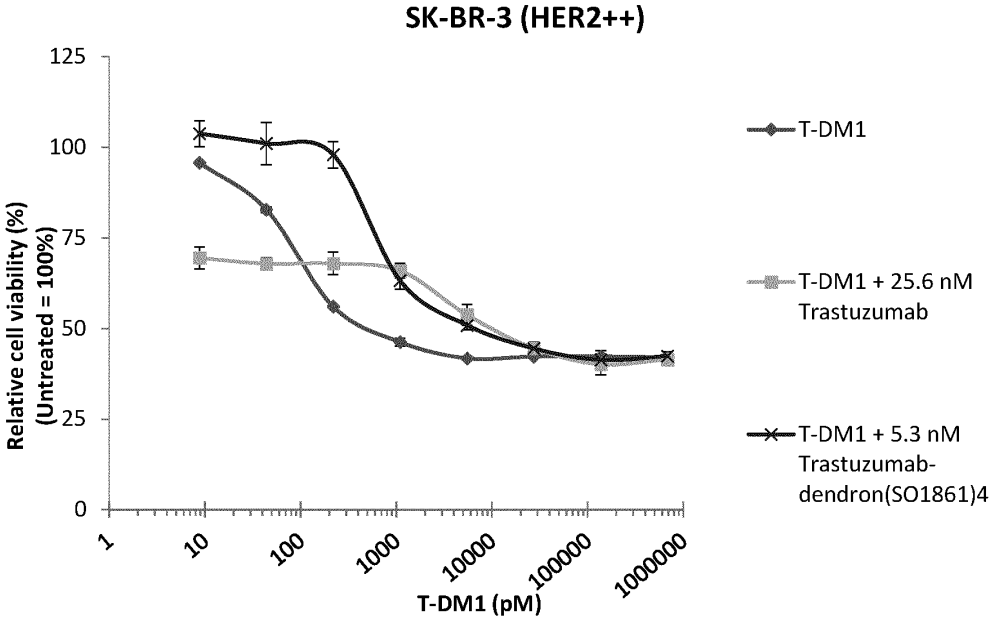


Figure 6-1

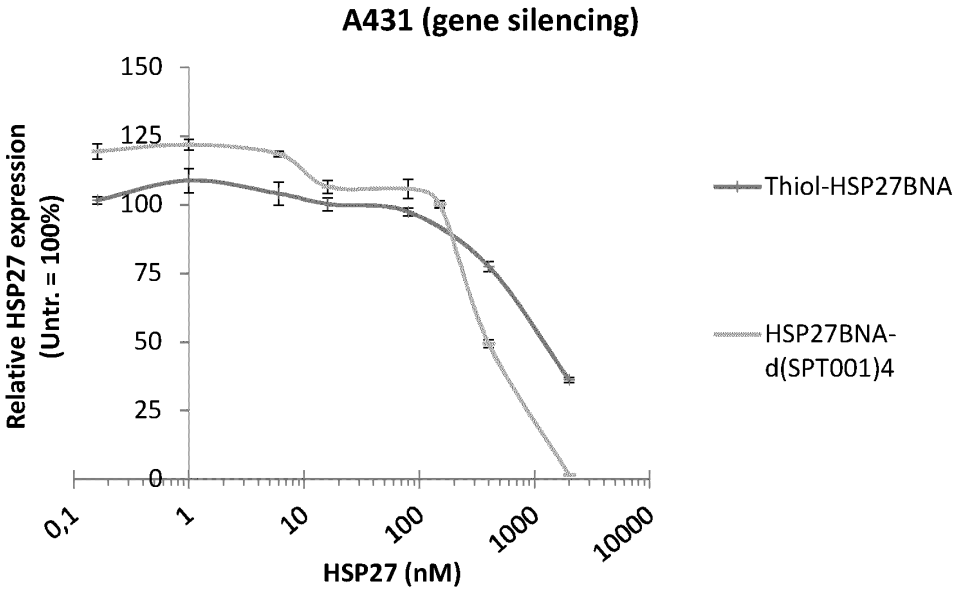

A431 (gene silencing)
Relative HSP27 expression (Untr. = 100%)
150
125
100
75
50
25
0
0,1
1
10
100
1000
10000
HSP27 (nM)
Thiol-HSP27BNA
HSP27BNA-d(SPT001)4

Figure 7-1

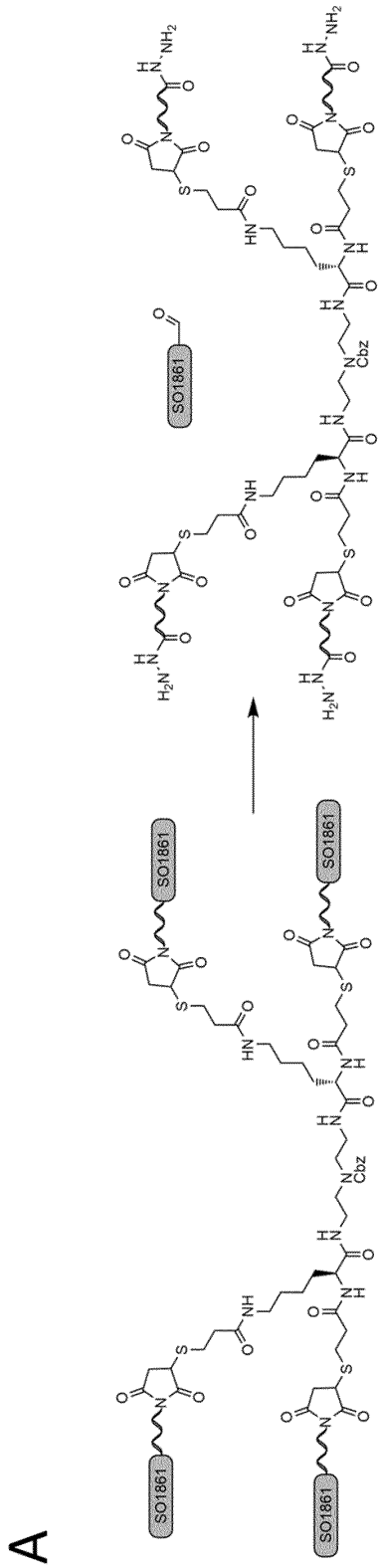
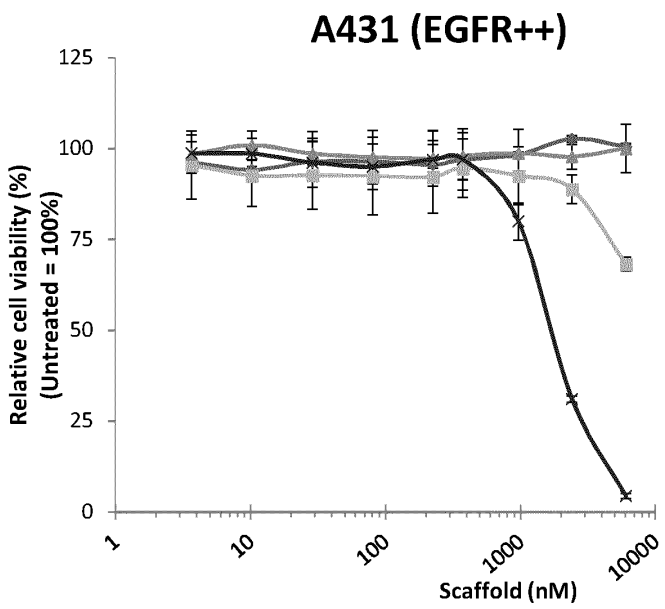


Figure 8-1

A


A431 (EGFR++)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
1
10
100
1000
10000
Scaffold (nM)

B

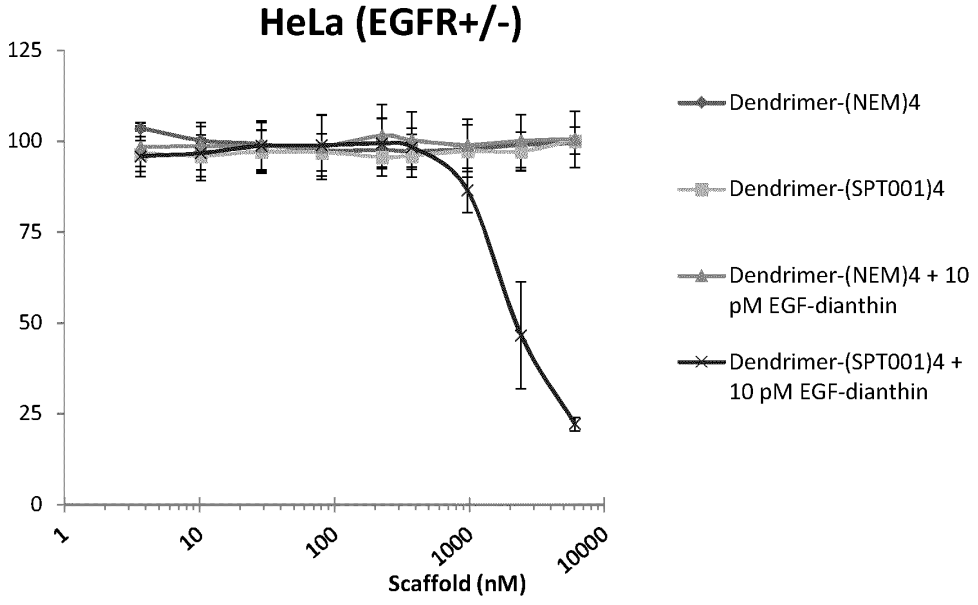
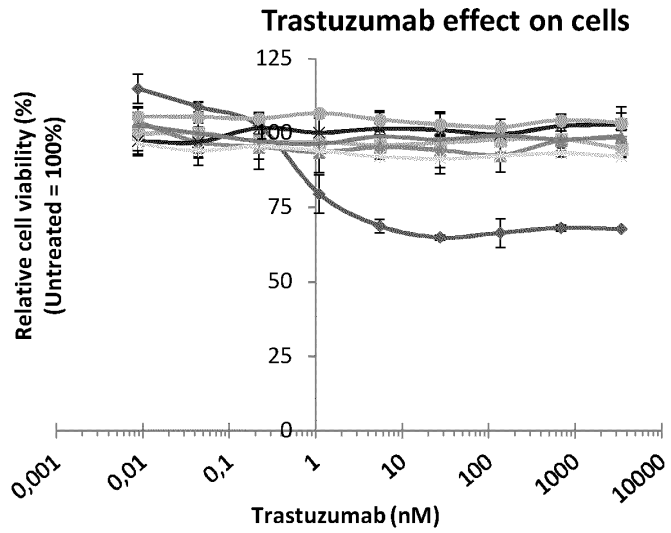

HeLa (EGFR+/-)
125
100
75
50
25
0
1
10
100
1000
10000
Scaffold (nM)
Dendrimer-(NEM)4
Dendrimer-(SPT001)4
Dendrimer-(NEM)4 + 10 pM EGF-dianthin
Dendrimer-(SPT001)4 + 10 pM EGF-dianthin

Figure 9-1

A


Trastuzumab effect on cells
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,001
0,01
0,1
1
10
100
1000
10000
Trastuzumab (nM)

B

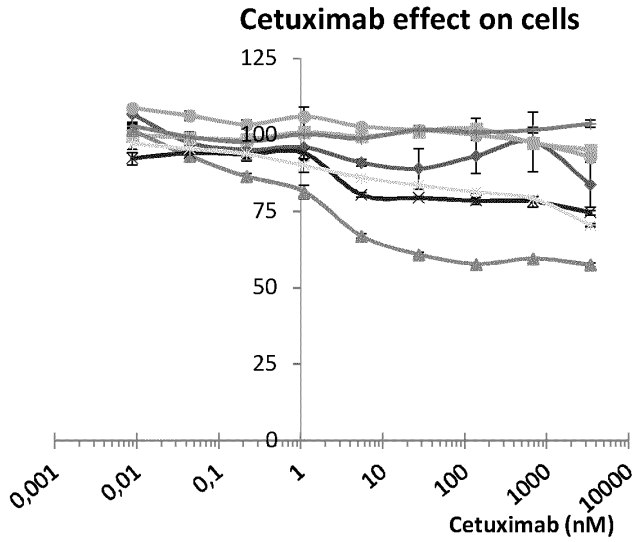

Cetuximab effect on cells
125
100
75
50
25
0
0,001
0,01
0,1
1
10
100
1000
10000
Cetuximab (nM)

Figure 9-1
C

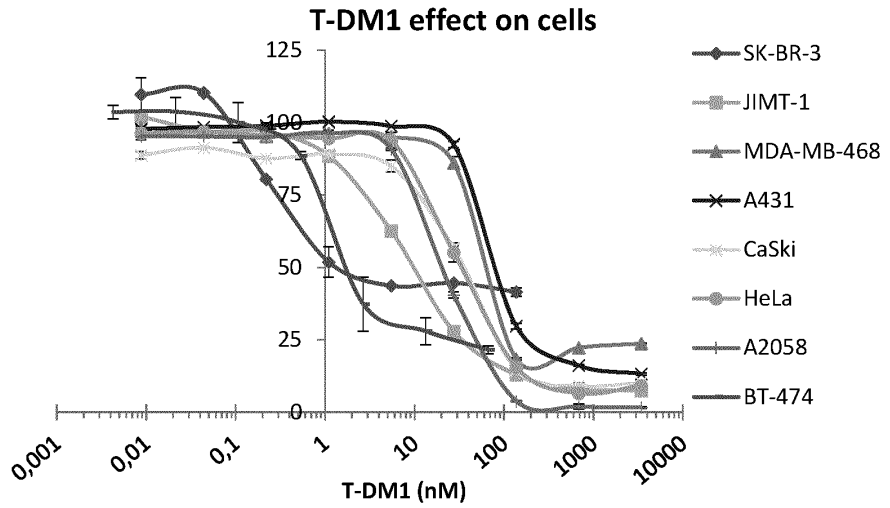


Figure 10-1

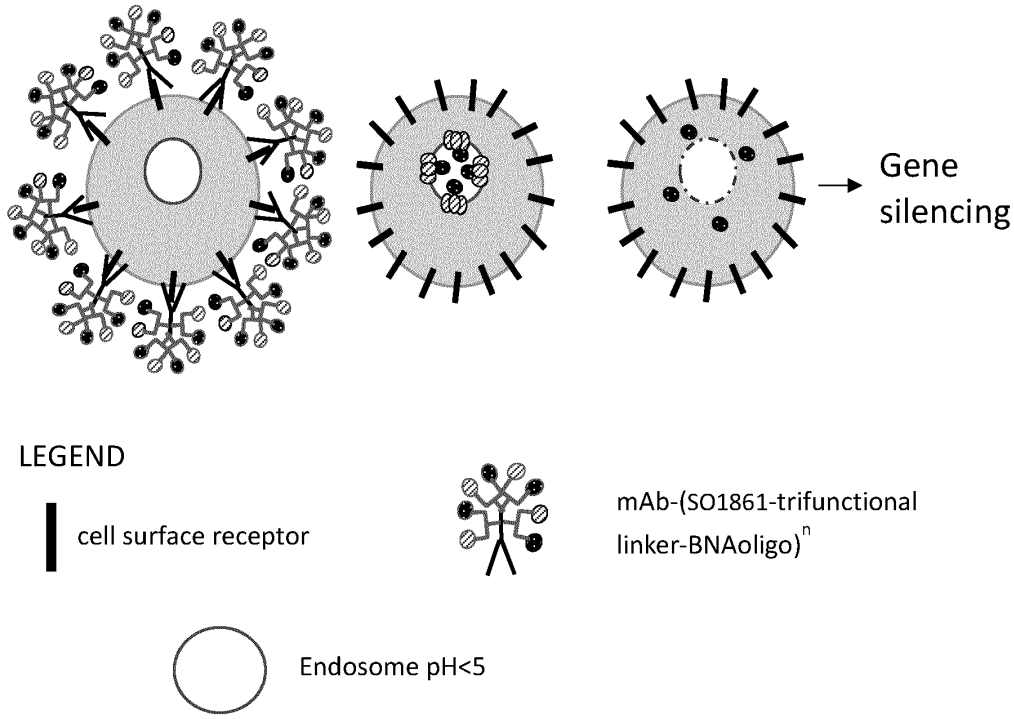


Figure 11-1

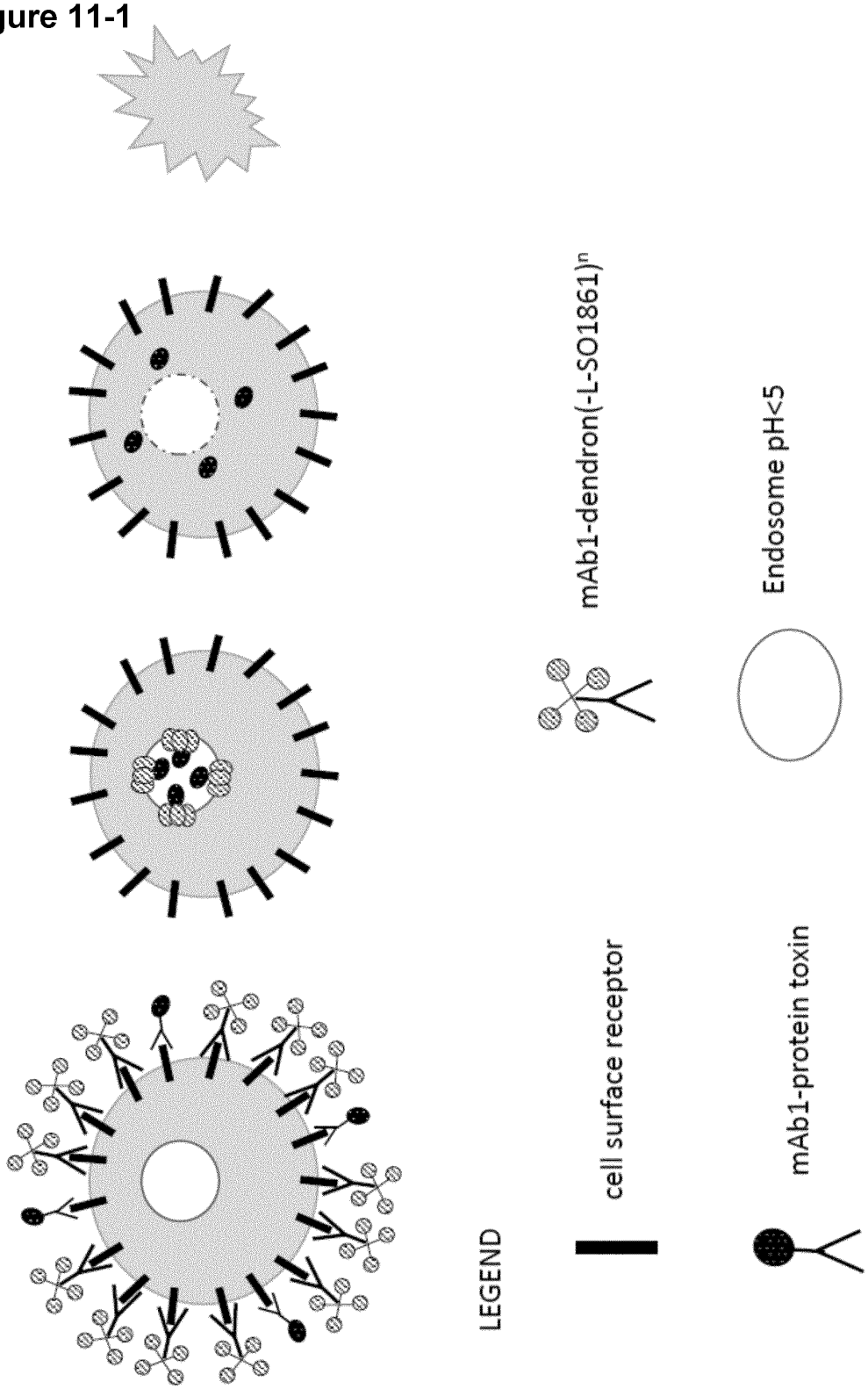

LEGEND
cell surface receptor
mAb1-protein toxin
mAb1-dendron(-L-SO1861)n
Endosome pH<5

Figure 12-1

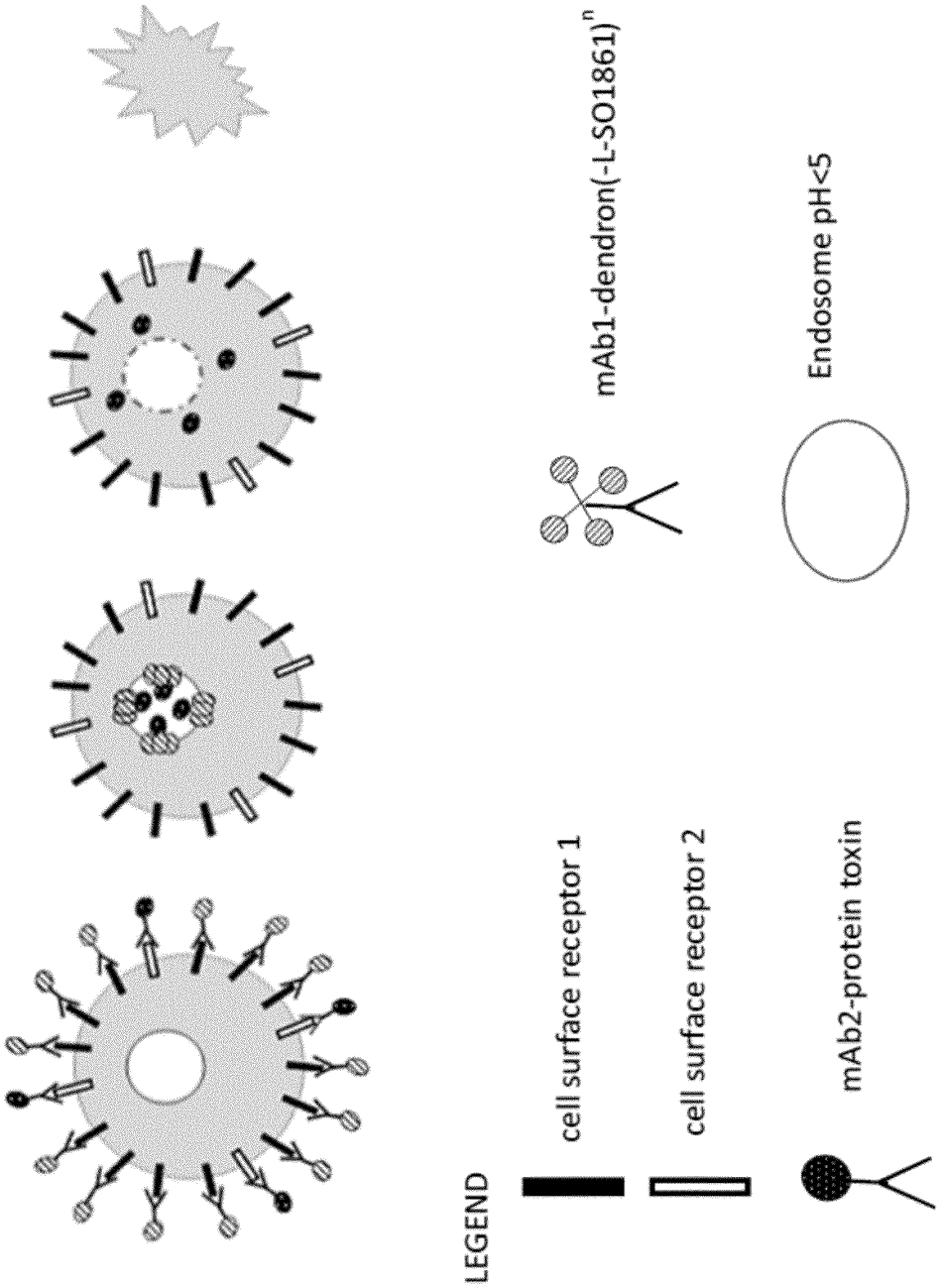

LEGEND
cell surface receptor 1
cell surface receptor 2
mAb2-protein toxin
mAb1-dendron(-L-SO1861)n
Endosome pH<5

Figure 13-1

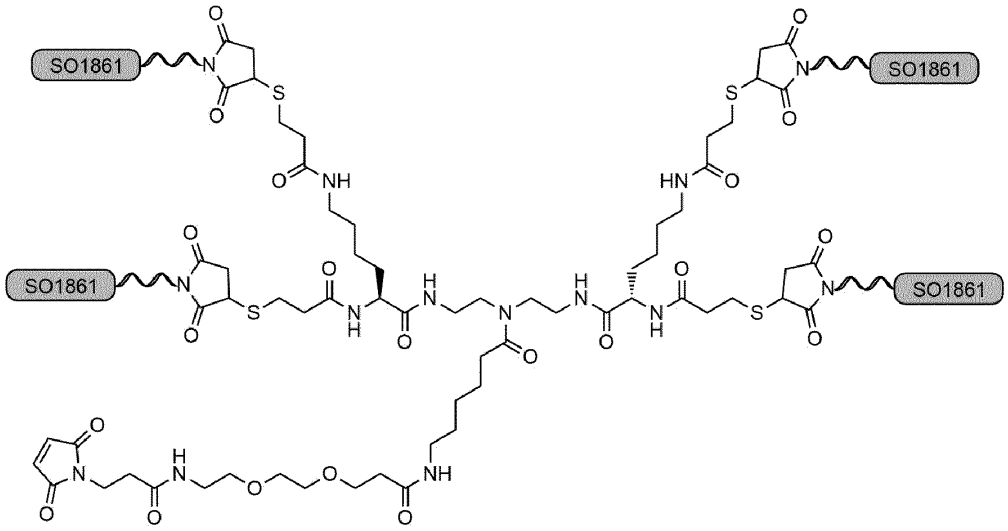


Figure 14-1

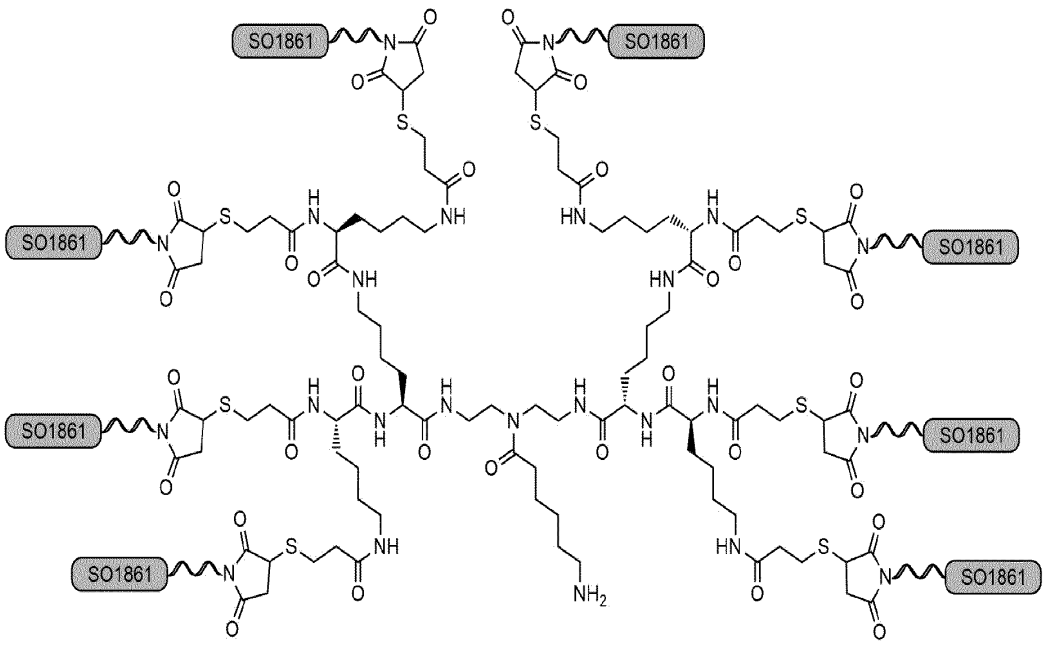


Figure 15-1

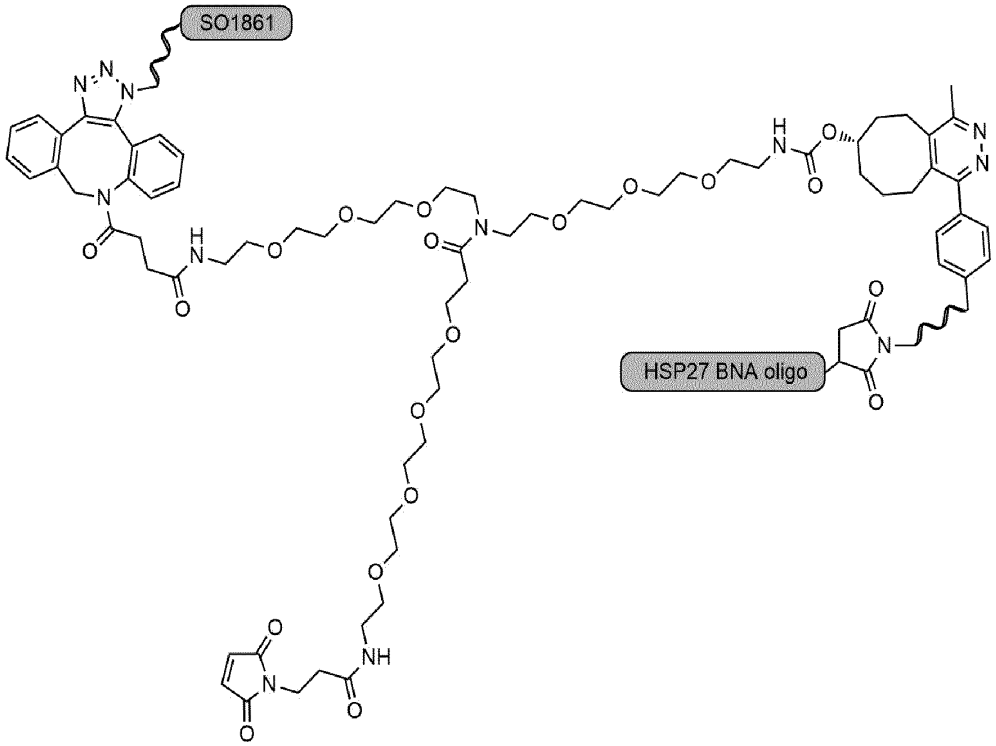


Figure 16-1

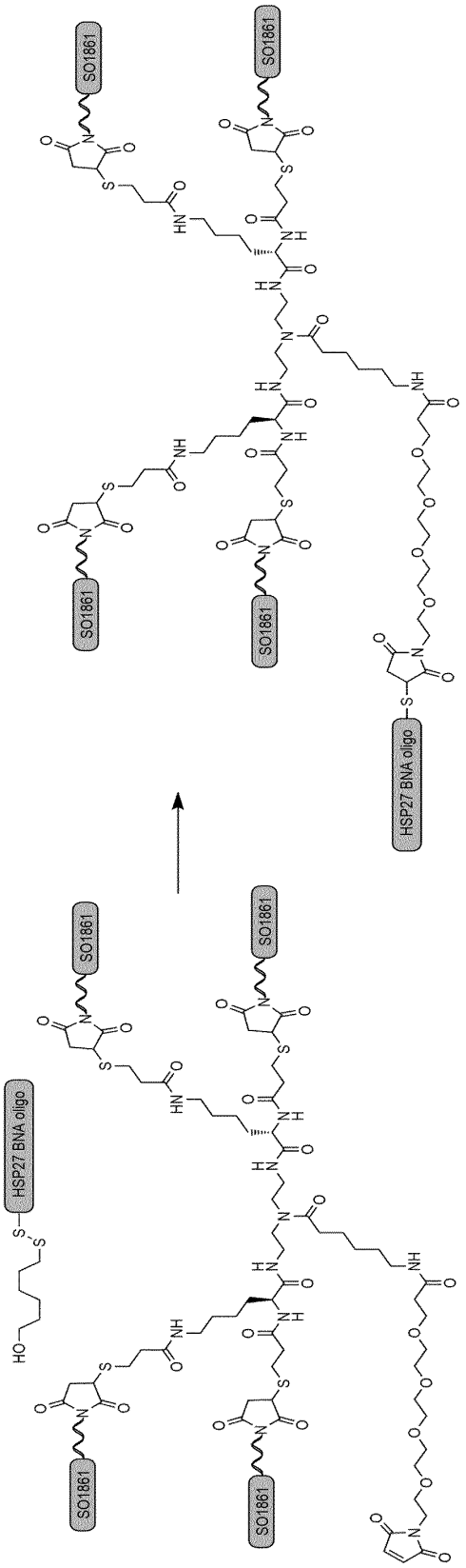


Figure 17-1

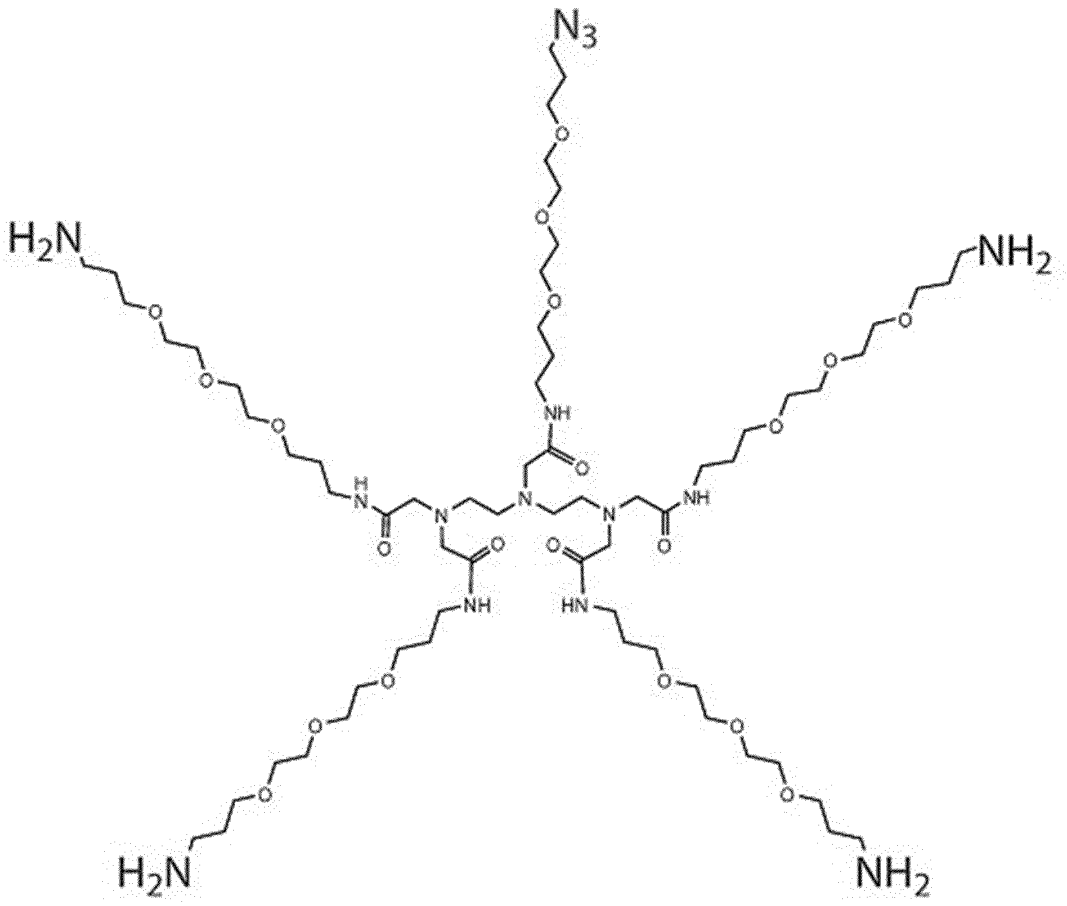


Figure 18-1

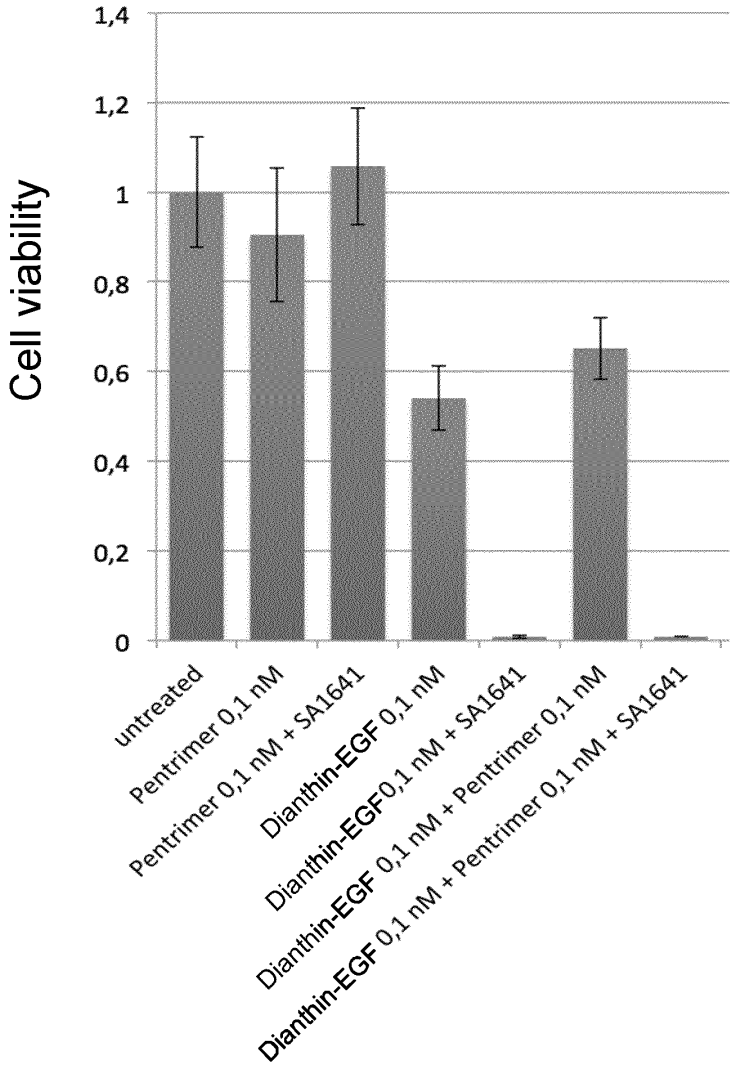

Cell viability
1,4
1,2
1
0,8
0,6
0,4
0,2
0
untreated
Pentrimer 0,1 nM
Pentrimer 0,1 nM + SA1641
Dianthin-EGF 0,1 nM
Dianthin-EGF 0,1 nM + SA1641
Dianthin-EGF 0,1 nM + Pentrimer 0,1 nM
Dianthin-EGF 0,1 nM + Pentrimer 0,1 nM + SA1641

Figure 19-1

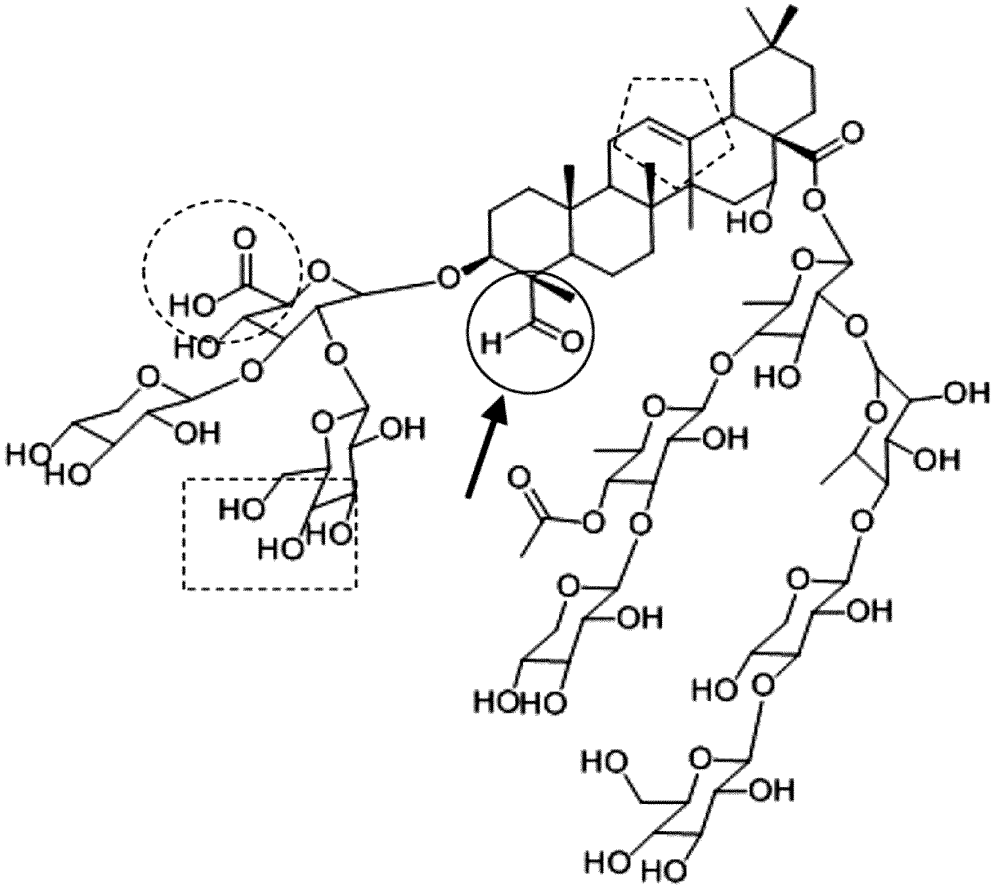
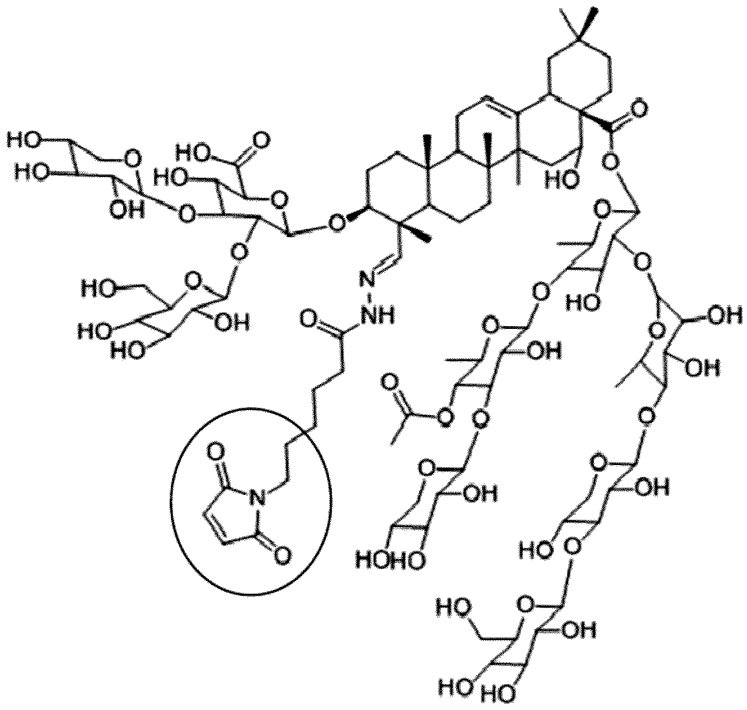


Figure 20-1

A



B

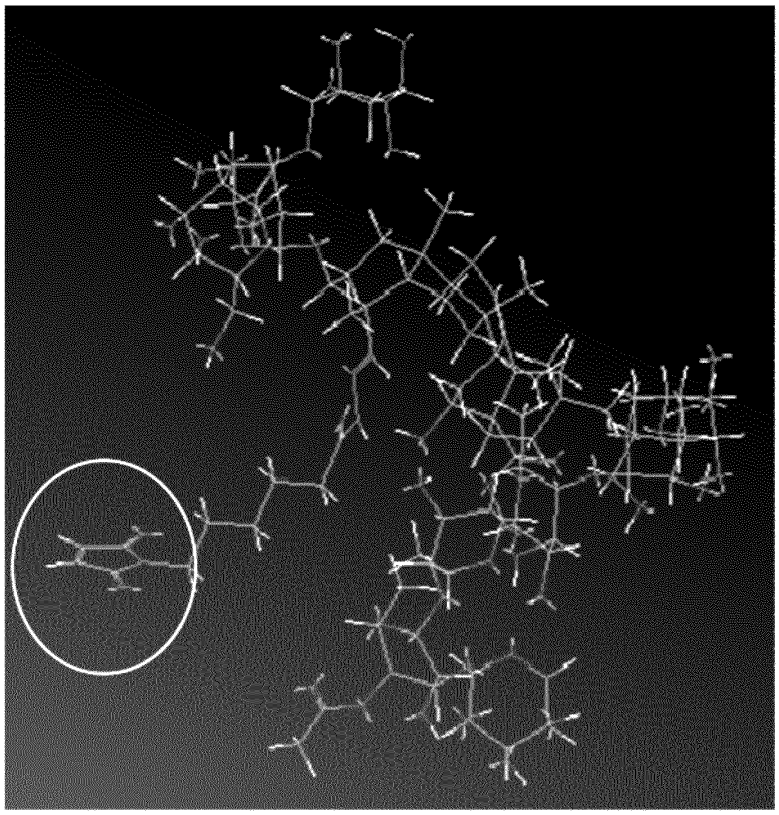


Figure 21-1

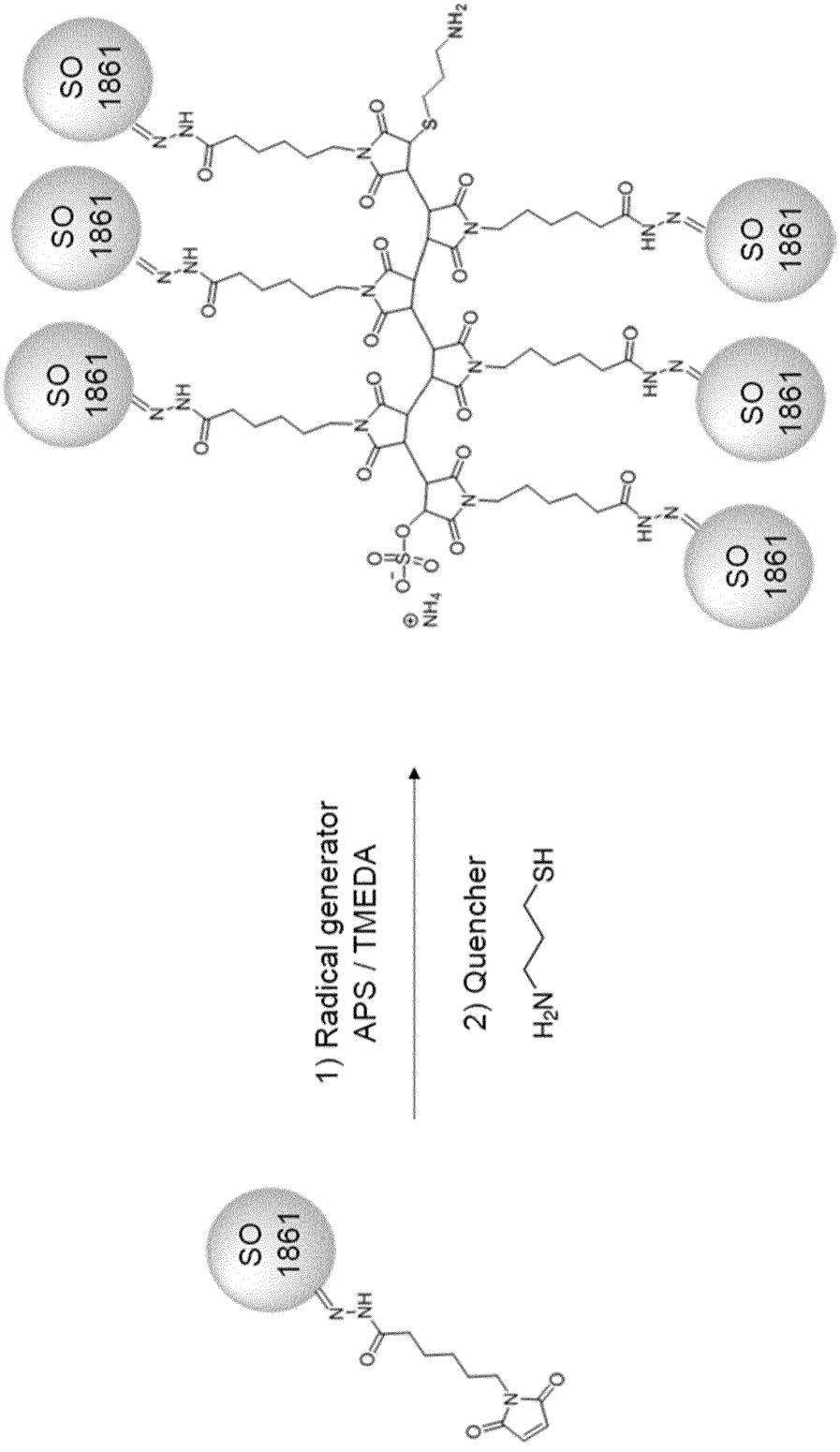


Figure 22-1

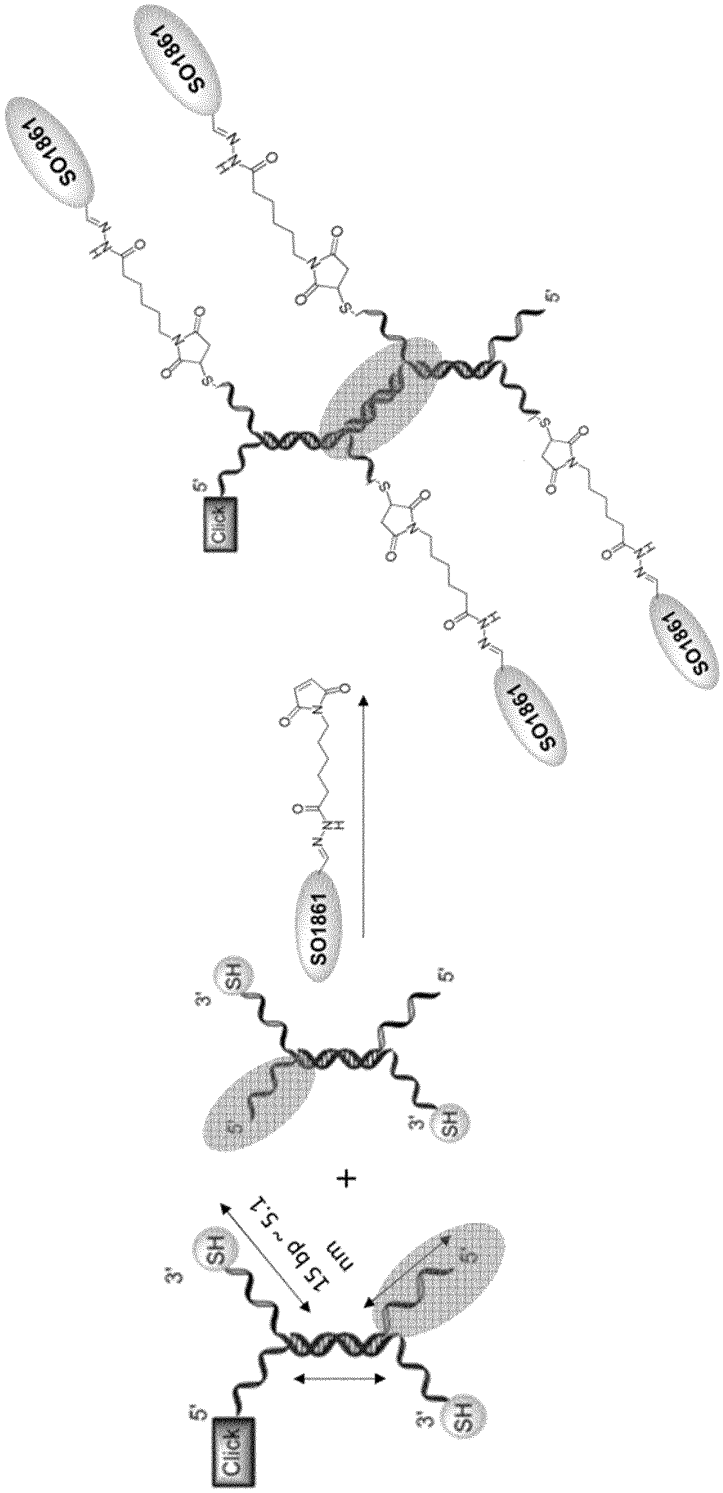

SO1861
SO1861
SO1861
SO1861
SO1861
5'
Click
5'
SO1861
SH
3'
5'
5'
3'
SH
+
SH
3'
15 bp ~ 5.1
nm
5'
5'
Click
3'
SH

Figure 23-1

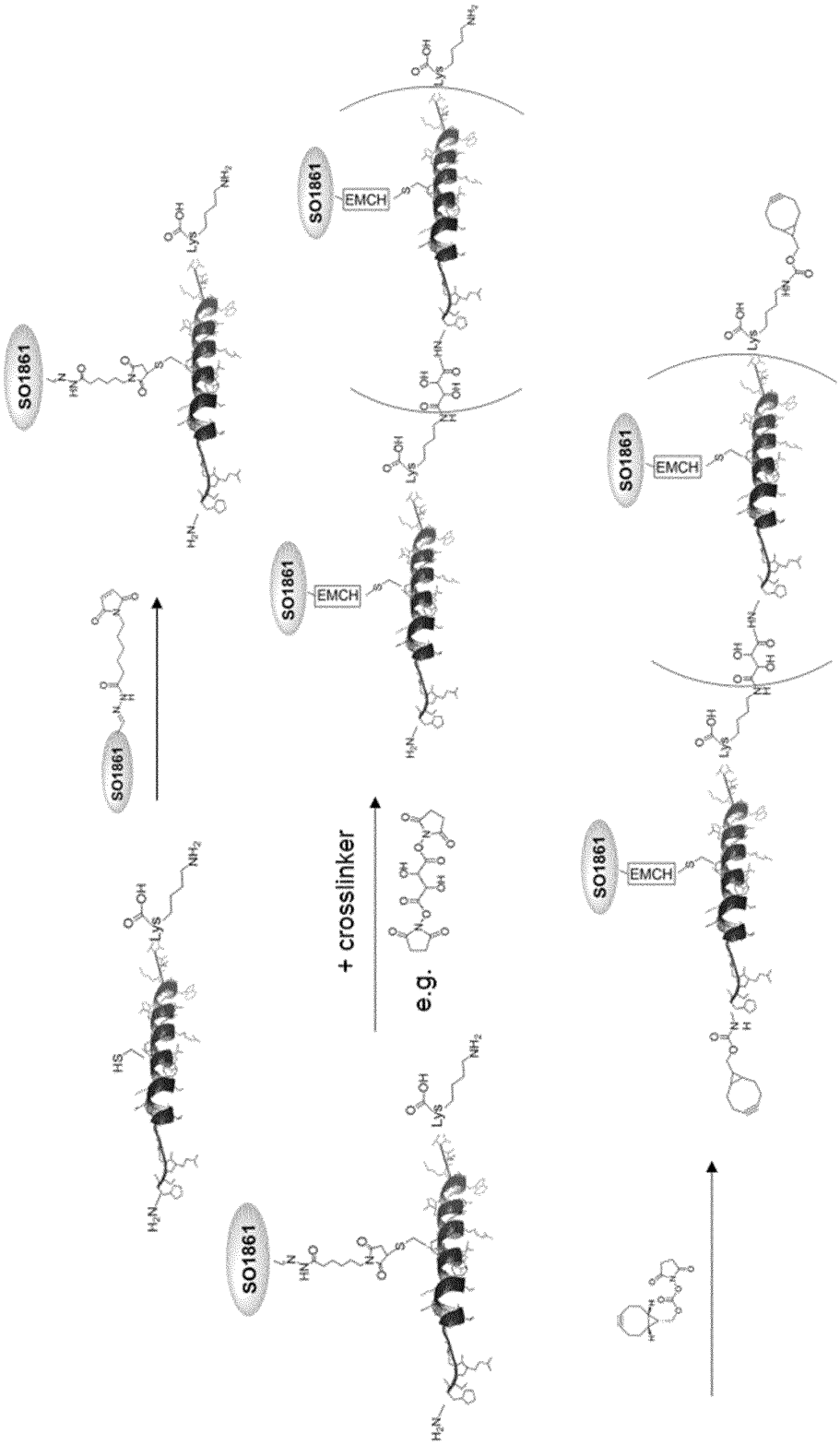


Figure 24-1

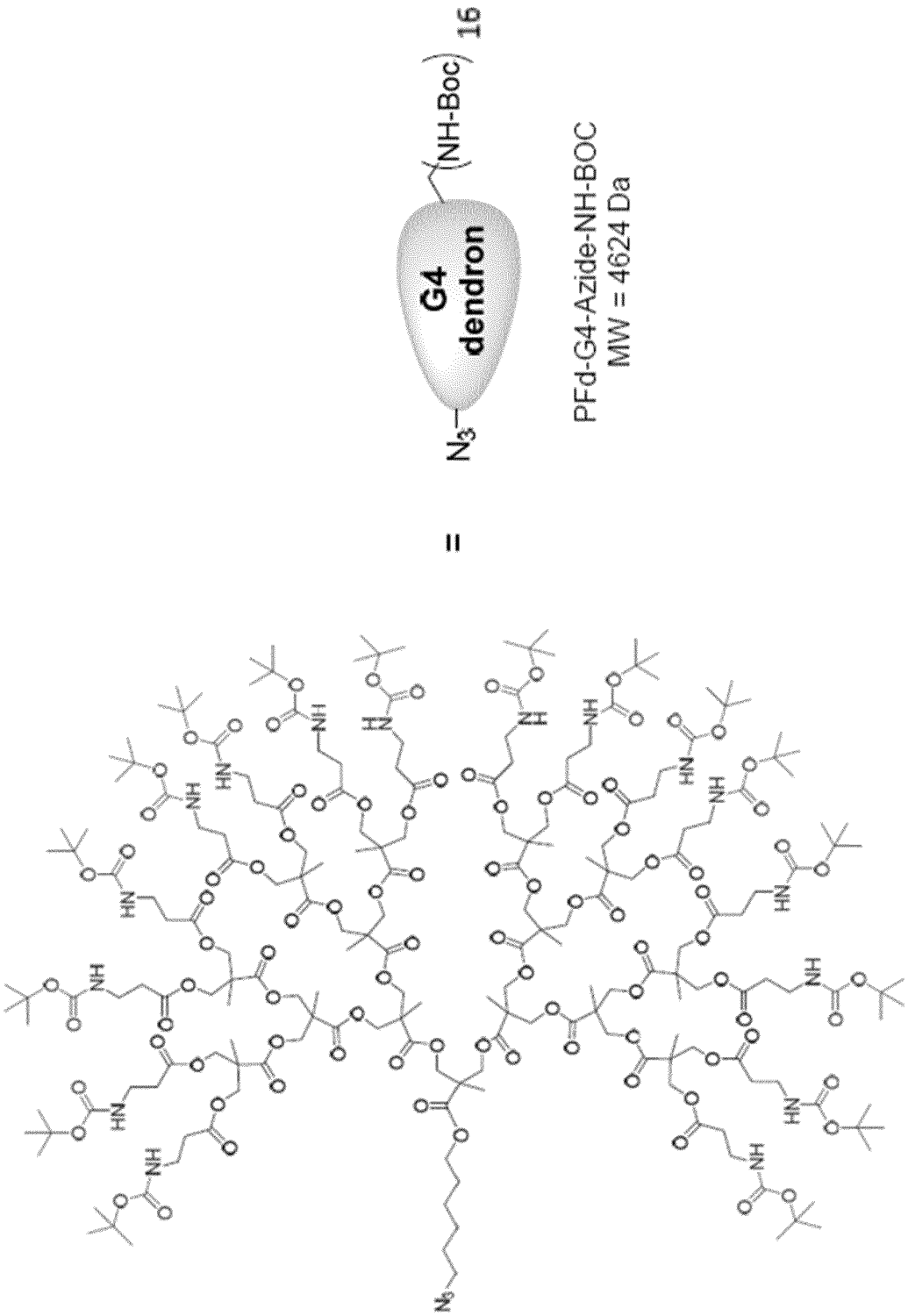


Figure 25-1

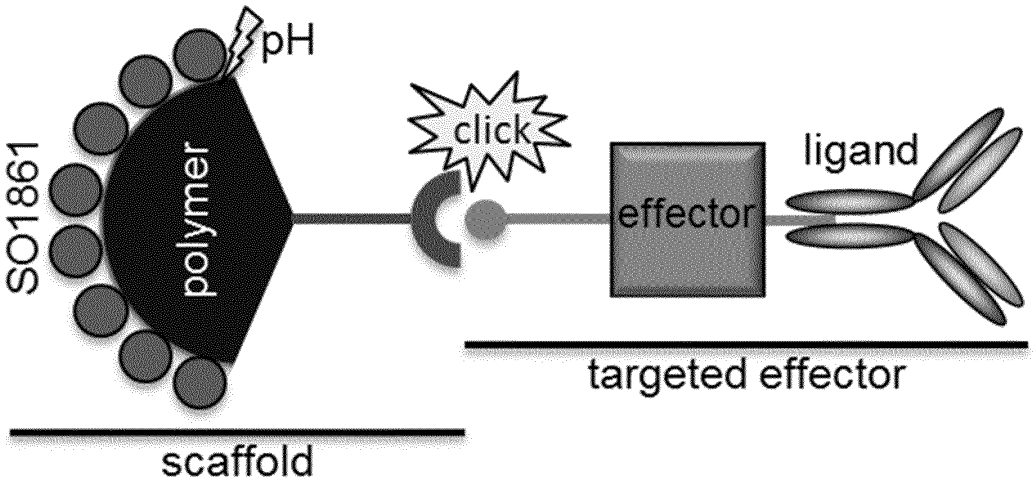

pH
SO1861
polymer
click
effector
ligand
targeted effector
scaffold

Figure 26-1

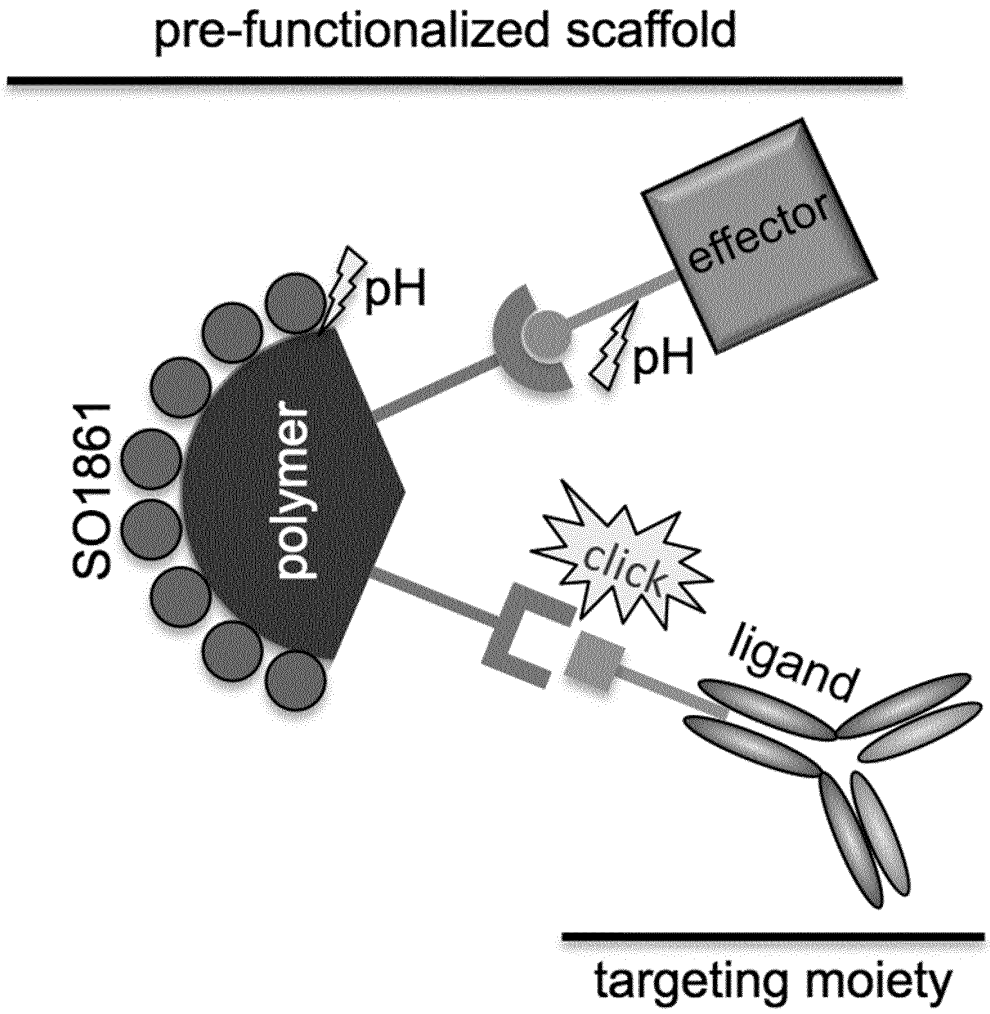

pre-functionalized scaffold
effector
pH
pH
SO1861
polymer
click
ligand
targeting moiety

FIGURE 1-2

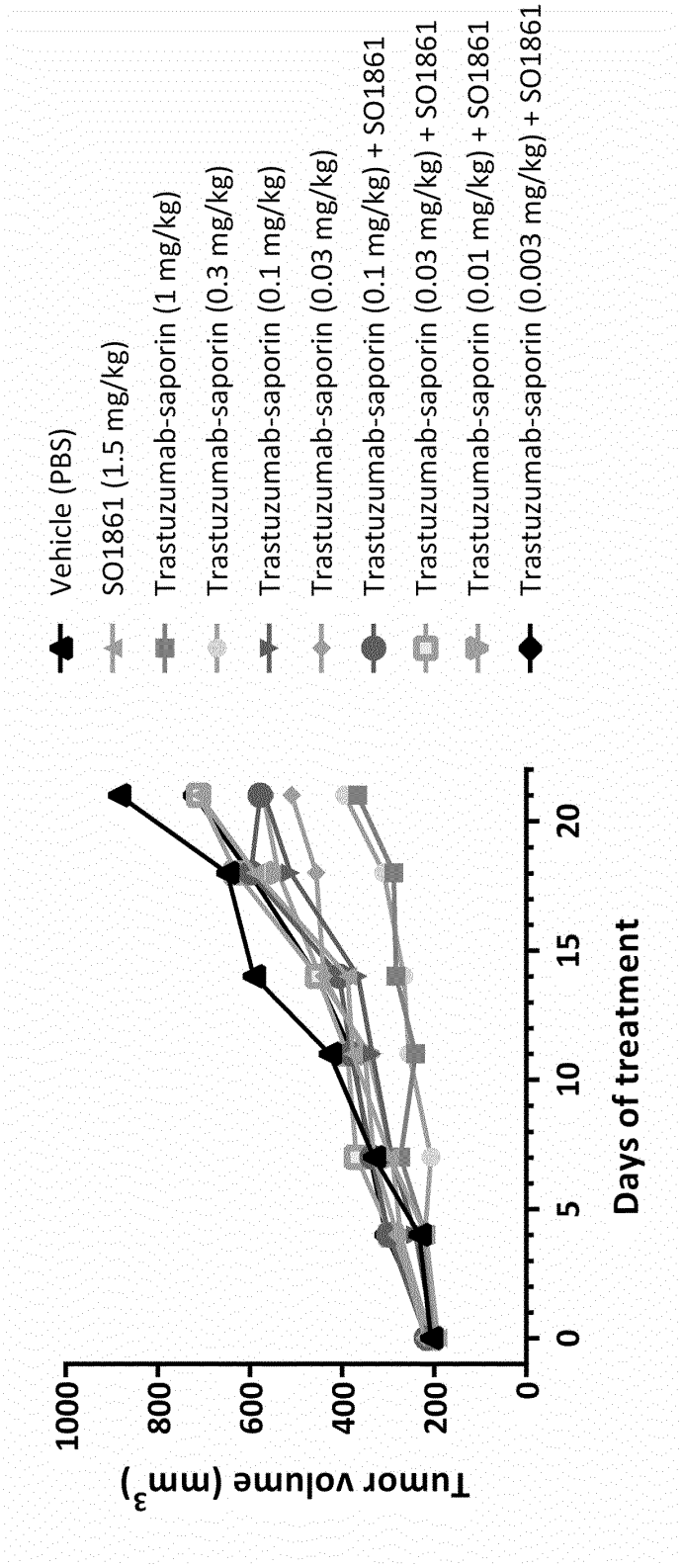
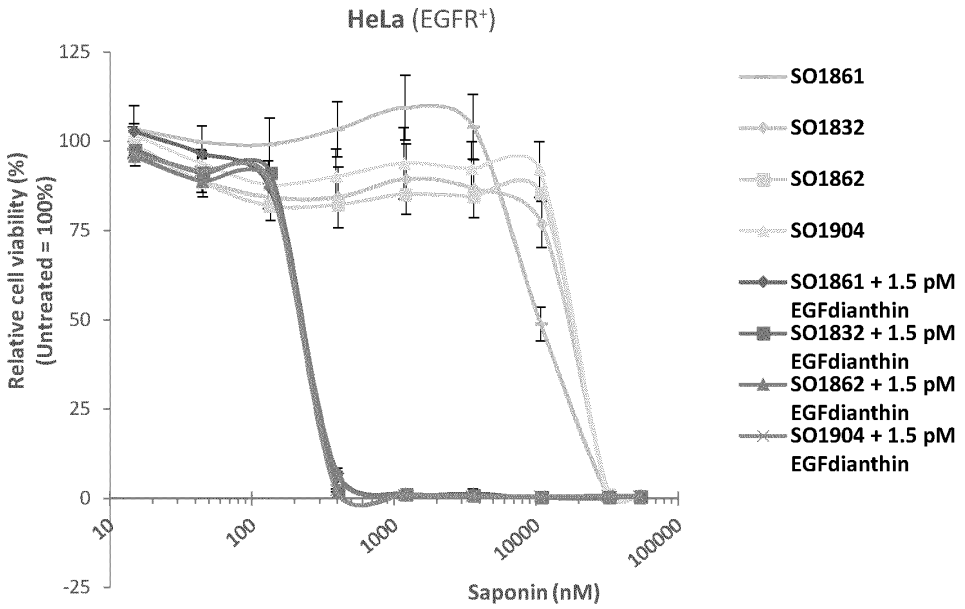

Vehicle (PBS)
SO1861 (1.5 mg/kg)
Trastuzumab-saporin (1 mg/kg)
Trastuzumab-saporin (0.3 mg/kg)
Trastuzumab-saporin (0.1 mg/kg)
Trastuzumab-saporin (0.03 mg/kg)
Trastuzumab-saporin (0.1 mg/kg) + SO1861
Trastuzumab-saporin (0.03 mg/kg) + SO1861
Trastuzumab-saporin (0.01 mg/kg) + SO1861
Trastuzumab-saporin (0.003 mg/kg) + SO1861
Tumor volume (mm3)
1000
800
600
400
200
0
0
5
10
15
20
Days of treatment

FIGURE 2-2

A.


HeLa (EGFR+)
Relative cell viability (%) (Untreated = 100%)
125
100
75
50
25
0
-25
10
100
1000
10000
100000
Saponin (nM)
SO1861
SO1832
SO1862
SO1904
SO1861 + 1.5 pM EGFdianthin
SO1832 + 1.5 pM EGFdianthin
SO1862 + 1.5 pM EGFdianthin
SO1904 + 1.5 pM EGFdianthin

B.

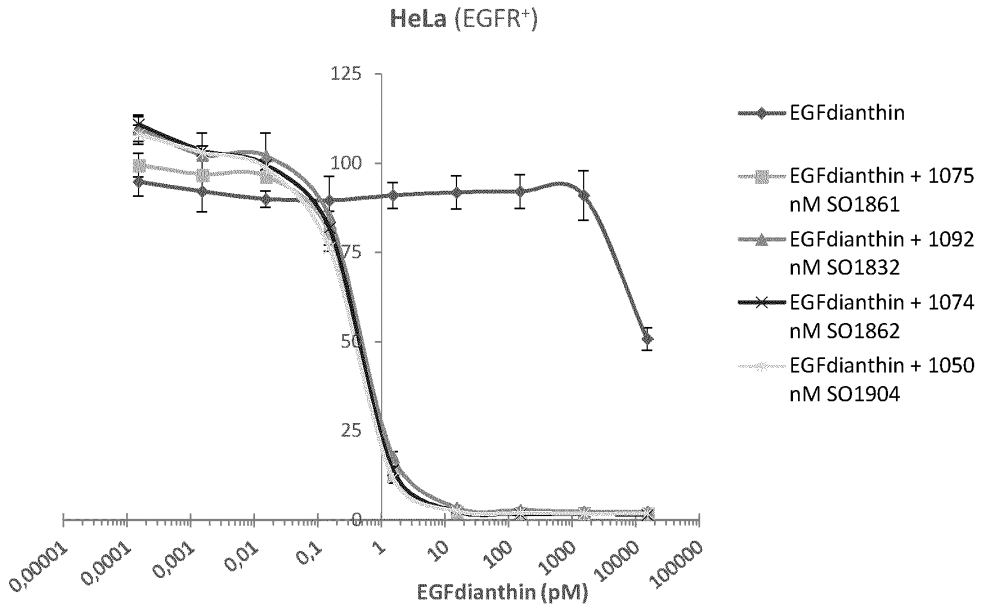
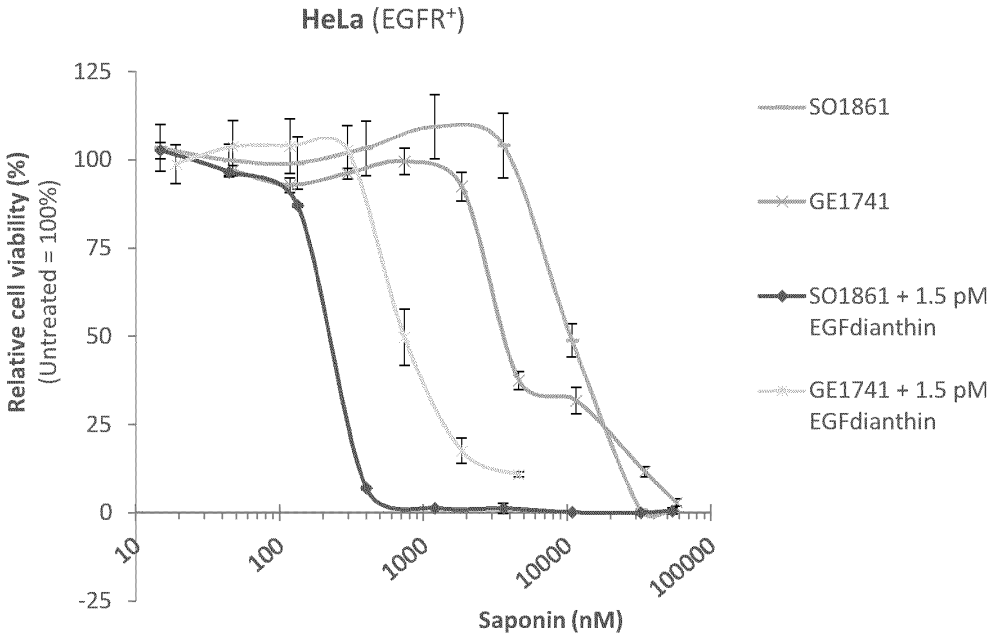

HeLa (EGFR+)
125
100
75
50
25
0
0,00001
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
100000
EGFdianthin (pM)
EGFdianthin
EGFdianthin + 1075 nM SO1861
EGFdianthin + 1092 nM SO1832
EGFdianthin + 1074 nM SO1862
EGFdianthin + 1050 nM SO1904

FIGURE 2-2

C.


HeLa (EGFR+)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
-25
10
100
1000
10000
100000
Saponin (nM)
SO1861
GE1741
SO1861 + 1.5 pM EGFdianthin
GE1741 + 1.5 pM EGFdianthin

D.

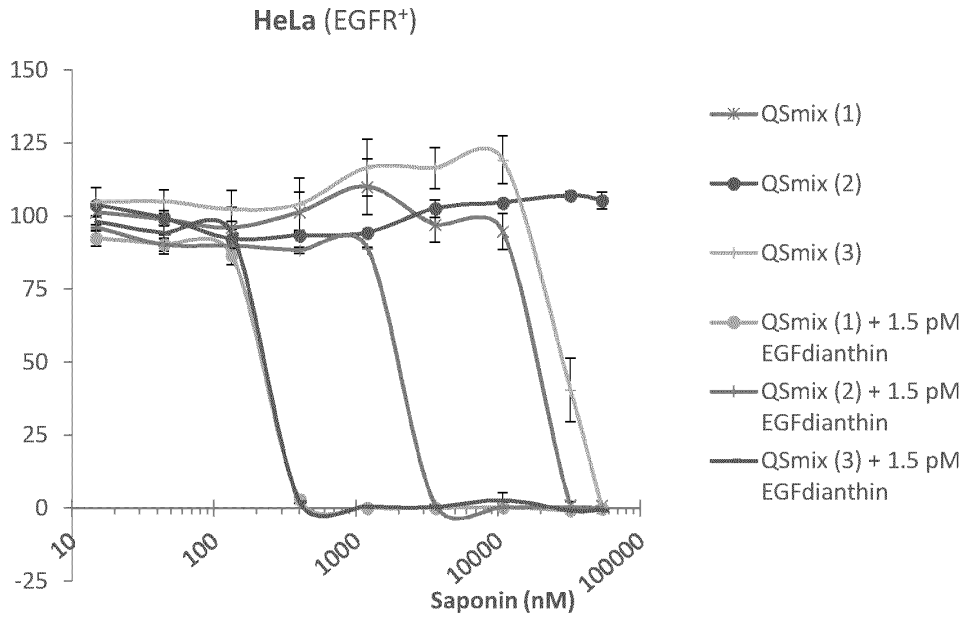
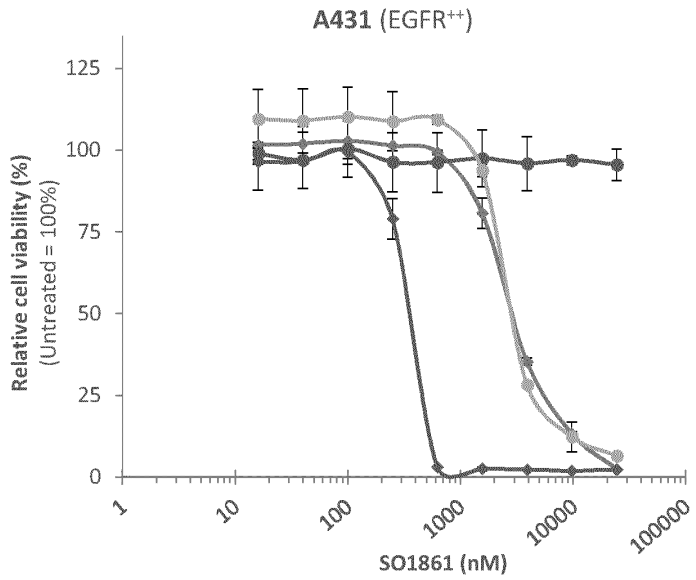

HeLa (EGFR+)
150
125
100
75
50
25
0
-25
10
100
1000
10000
100000
Saponin (nM)
QSmix (1)
QSmix (2)
QSmix (3)
QSmix (1) + 1.5 pM EGFdianthin
QSmix (2) + 1.5 pM EGFdianthin
QSmix (3) + 1.5 pM EGFdianthin

FIGURE 3-2

A.


A431 (EGFR++)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
1
10
100
1000
10000
100000
SO1861 (nM)

B.

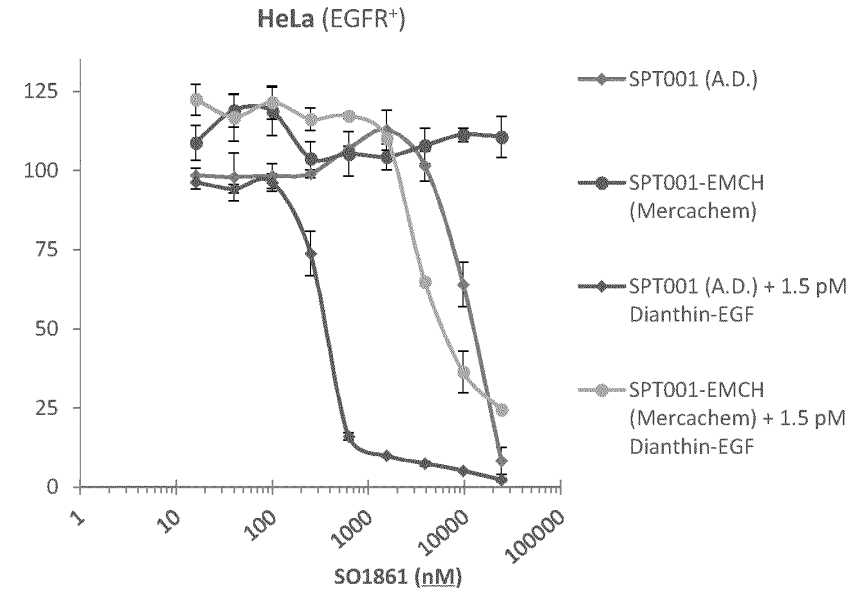
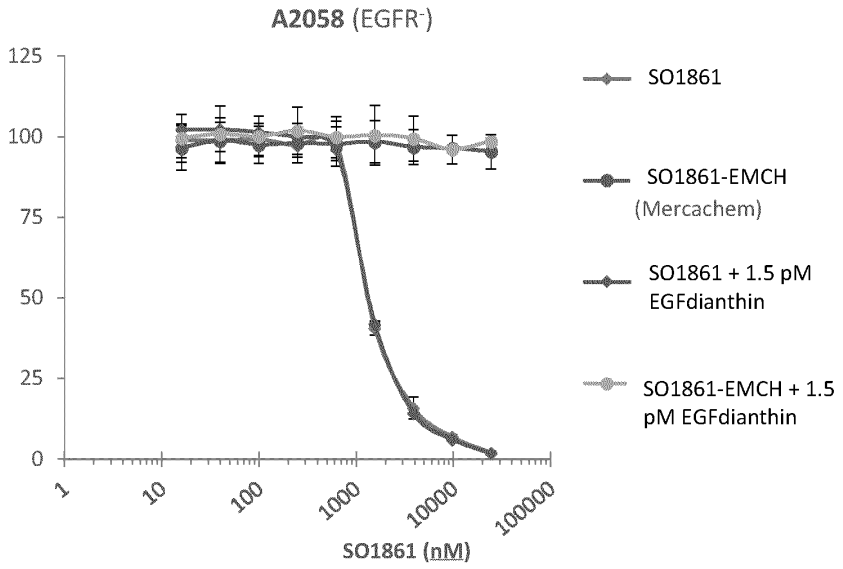

HeLa (EGFR+)
125
100
75
50
25
0
1
10
100
1000
10000
100000
SO1861 (nM)
SPT001 (A.D.)
SPT001-EMCH (Mercachem)
SPT001 (A.D.) + 1.5 pM Dianthin-EGF
SPT001-EMCH (Mercachem) + 1.5 pM Dianthin-EGF

FIGURE 3-2

C.


A2058 (EGFR-)
125
100
75
50
25
0
1
10
100
1000
10000
100000
SO1861 (nM)
SO1861
SO1861-EMCH
(Mercachem)
SO1861 + 1.5 pM
EGFdianthin
SO1861-EMCH + 1.5
pM EGFdianthin

D.

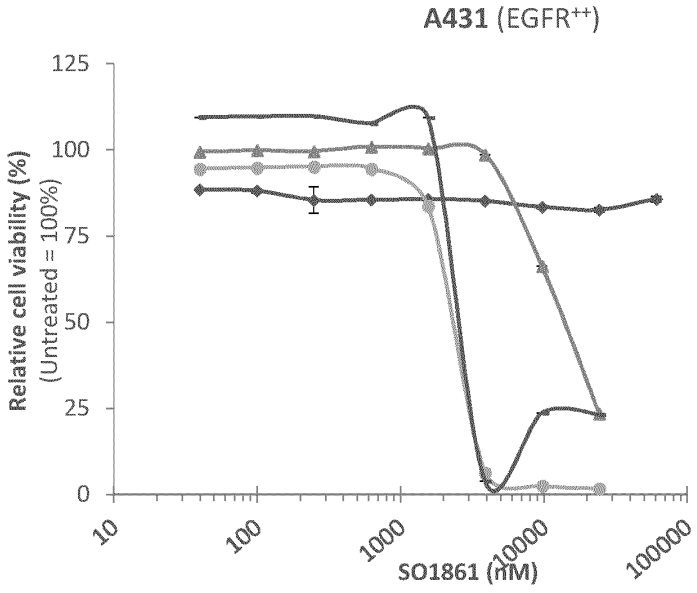

A431 (EGFR++)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
10
100
1000
10000
100000
SO1861 (nM)

FIGURE 3-2

E.

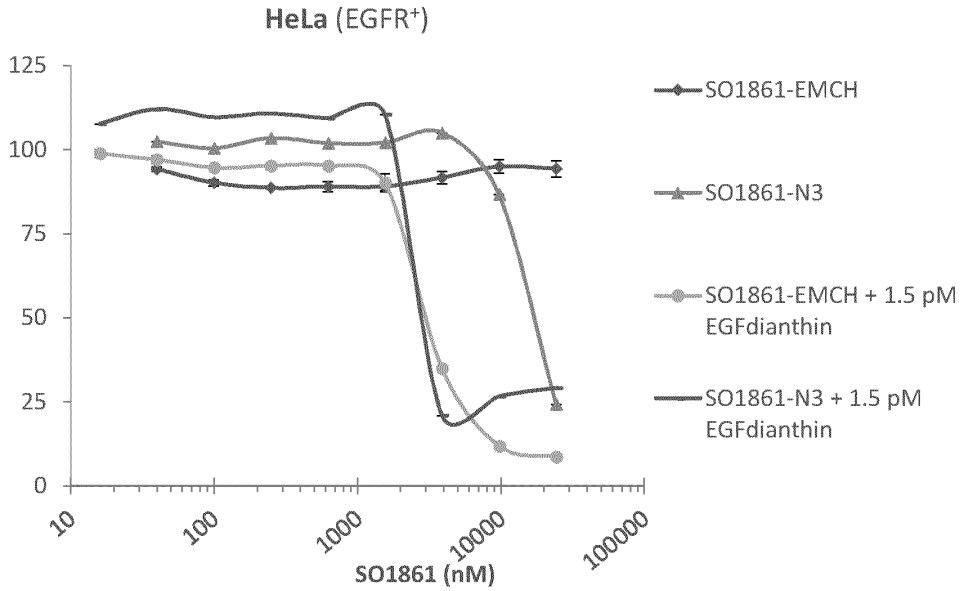


FIGURE 4-2

A.

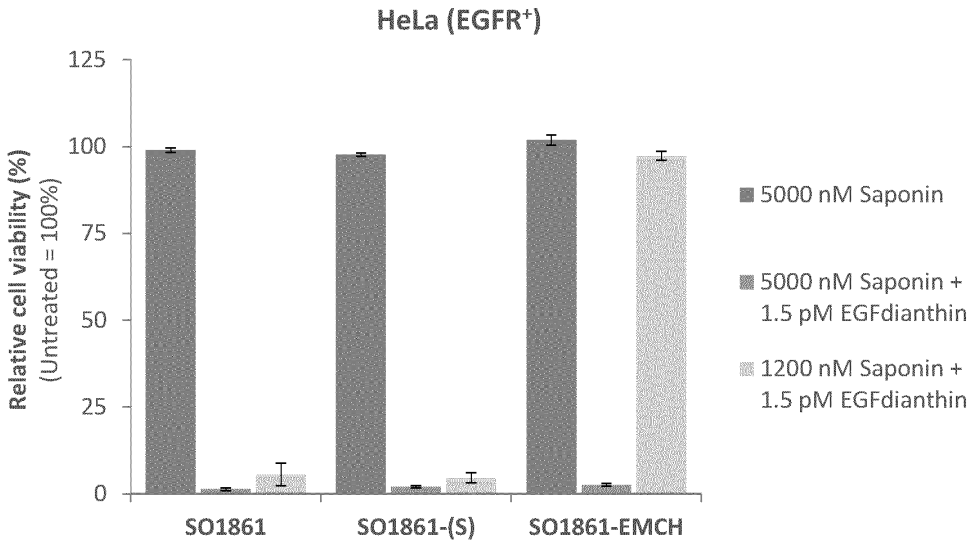
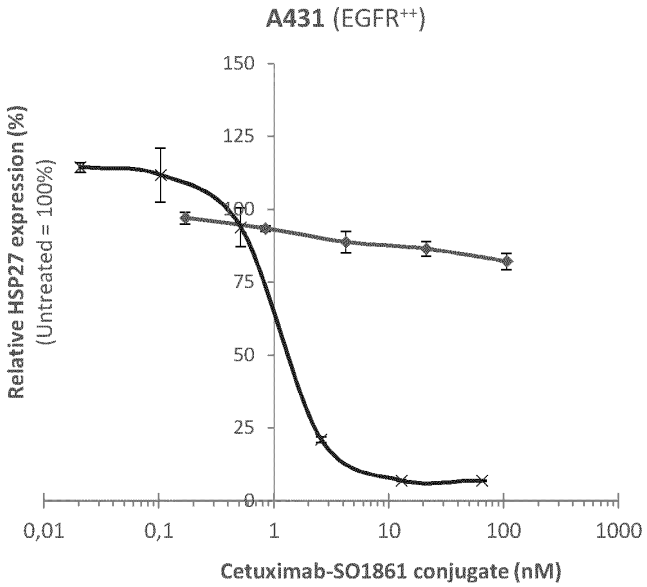


FIGURE 5-2

A.


A431 (EGFR++)
Relative HSP27 expression (%)
(Untreated = 100%)
150
125
100
75
50
25
0
0,01
0,1
1
10
100
1000
Cetuximab-SO1861 conjugate (nM)

B.

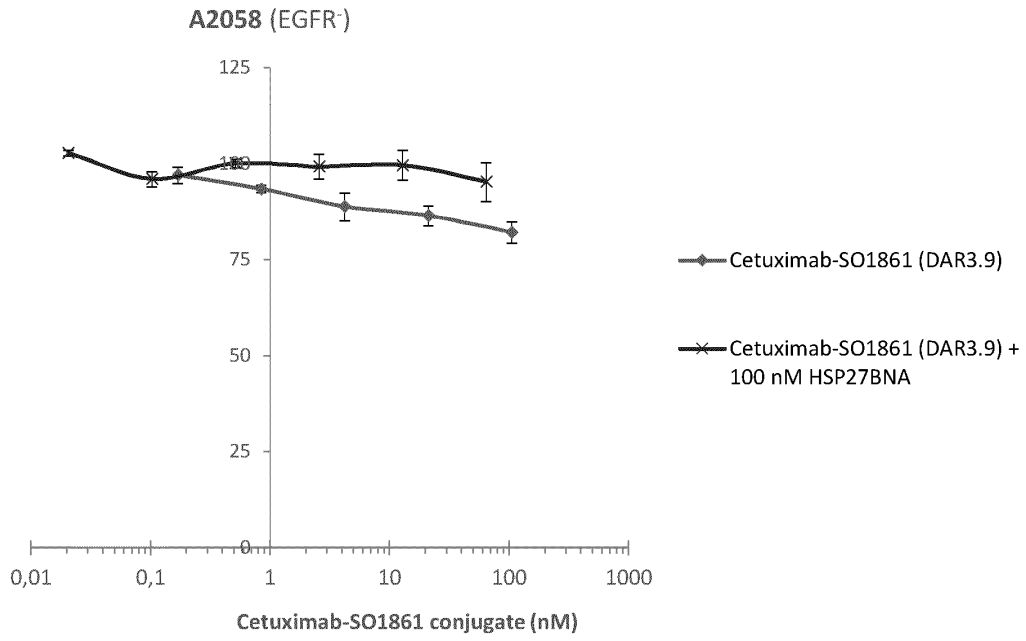
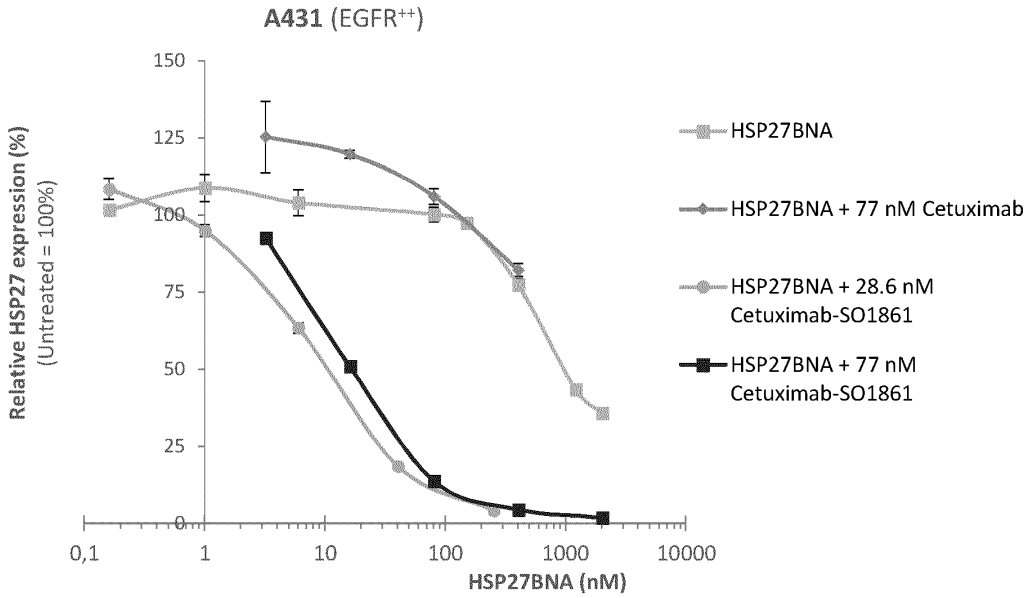

A2058 (EGFR-)
125
75
50
25
0
0,01
0,1
1
10
100
1000
Cetuximab-SO1861 conjugate (nM)
Cetuximab-SO1861 (DAR3.9)
Cetuximab-SO1861 (DAR3.9) + 100 nM HSP27BNA

FIGURE 5-2

C.


A431 (EGFR++)
Relative HSP27 expression (%)
(Untreated = 100%)
150
125
100
75
50
25
0
0,1
1
10
100
1000
10000
HSP27BNA (nM)
HSP27BNA
HSP27BNA + 77 nM Cetuximab
HSP27BNA + 28.6 nM Cetuximab-SO1861
HSP27BNA + 77 nM Cetuximab-SO1861

D.

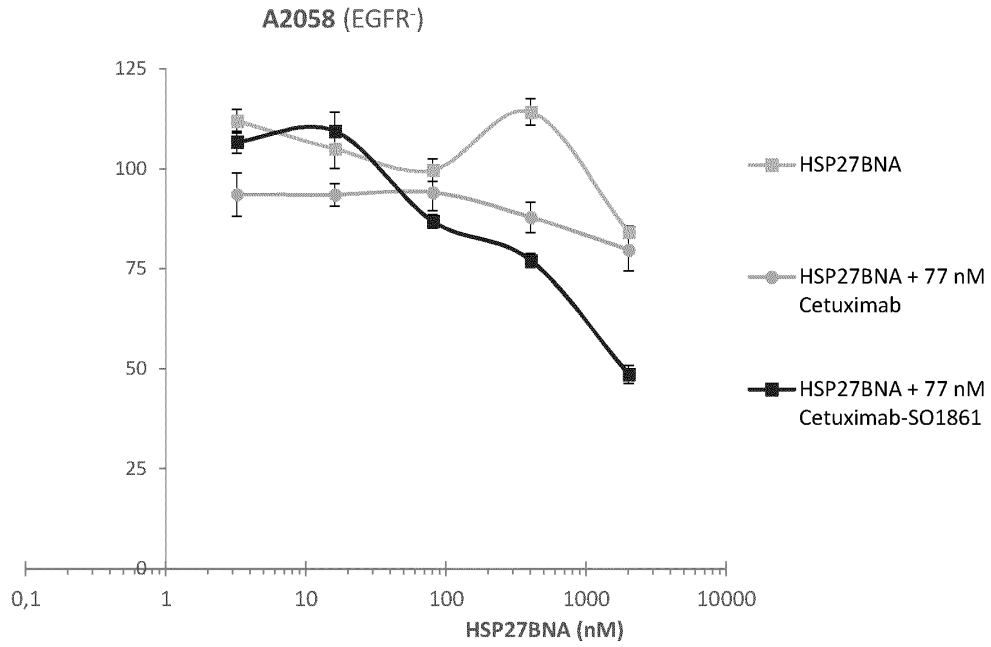

A2058 (EGFR-)
125
100
75
50
25
0
0,1
1
10
100
1000
10000
HSP27BNA (nM)
HSP27BNA
HSP27BNA + 77 nM Cetuximab
HSP27BNA + 77 nM Cetuximab-SO1861

FIGURE 6-2

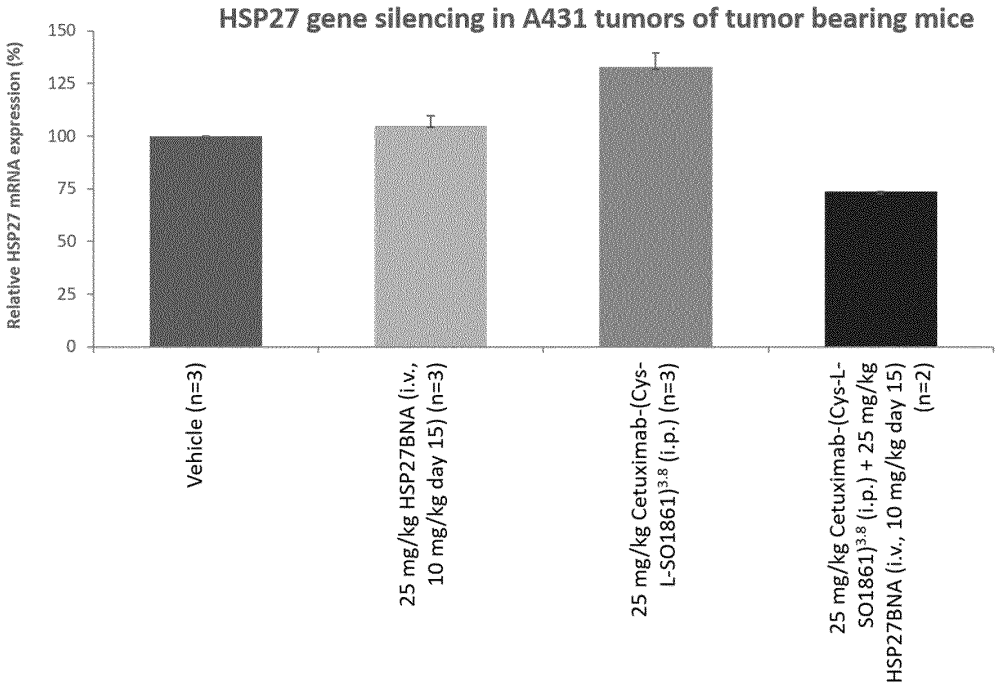

HSP27 gene silencing in A431 tumors of tumor bearing mice
Relative HSP27 mRNA expression (%)
150
125
100
75
50
25
0
Vehicle (n=3)
25 mg/kg HSP27BNA (i.v., 10 mg/kg day 15) (n=3)
25 mg/kg Cetuximab-(Cys-L-SO1861)3.8 (i.p.) (n=3)
25 mg/kg Cetuximab-(Cys-L-SO1861)3.8 (i.p.) + 25 mg/kg HSP27BNA (i.v., 10 mg/kg day 15) (n=2)

Figure 1-3

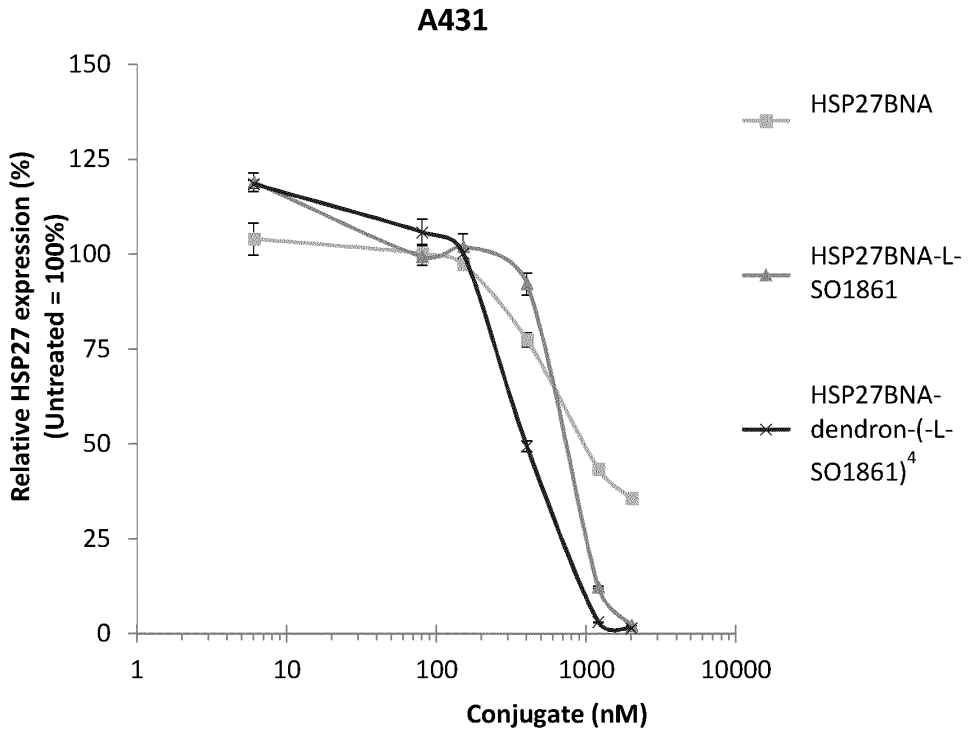

A431
Relative HSP27 expression (%)
(Untreated = 100%)
150
125
100
75
50
25
0
1
10
100
1000
10000
Conjugate (nM)
HSP27BNA
HSP27BNA-L-SO1861
HSP27BNA-dendron-(-L-SO1861)4

Figure 1-4

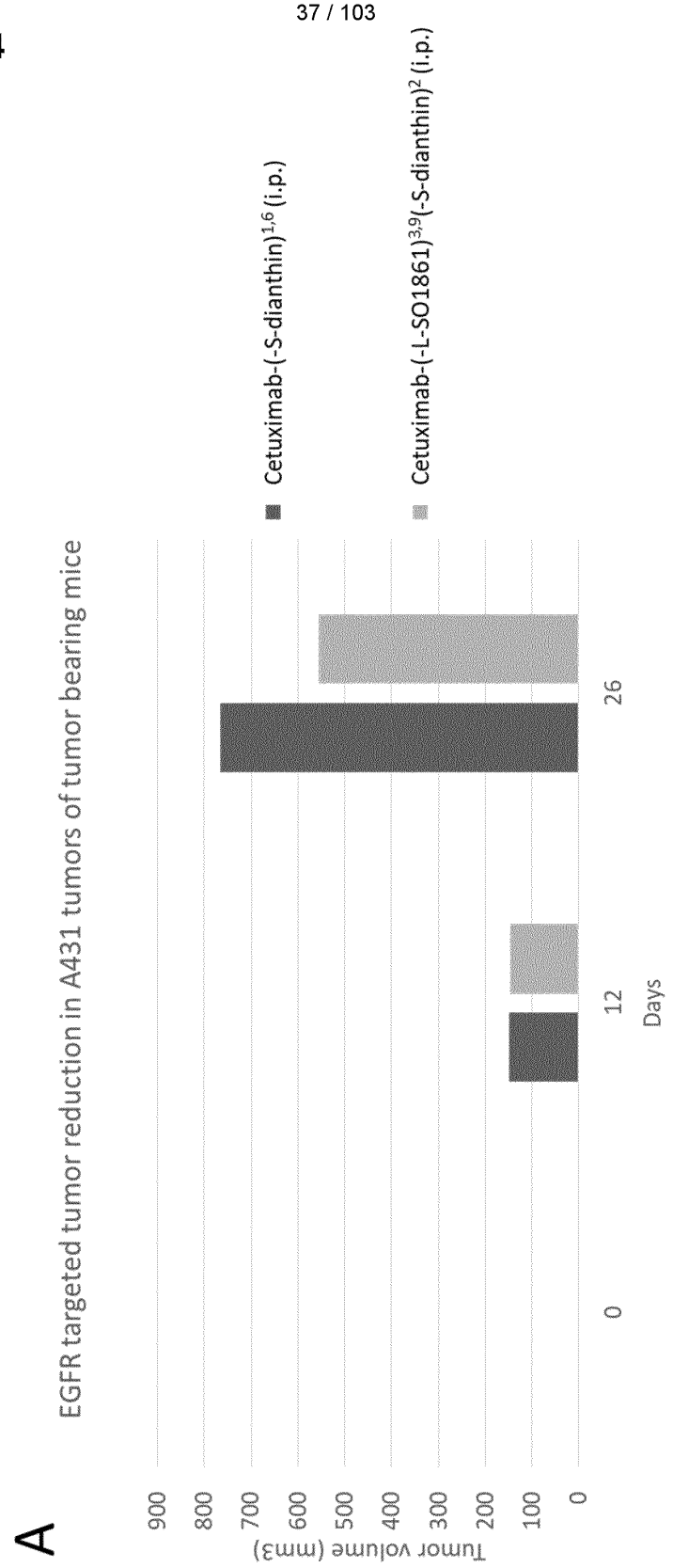
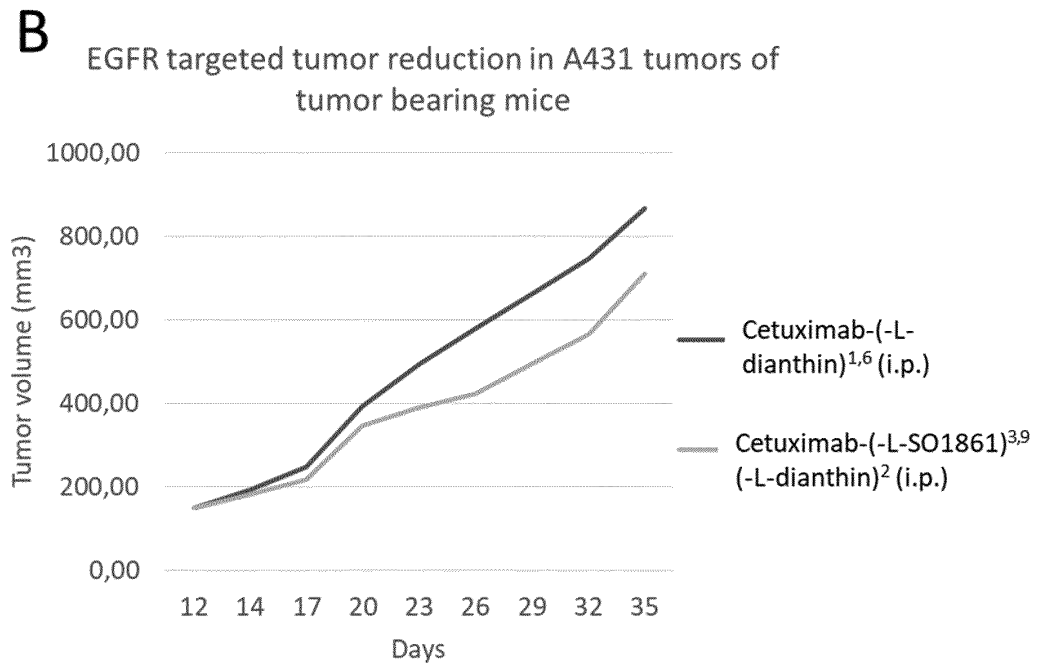

A
EGFR targeted tumor reduction in A431 tumors of tumor bearing mice
Tumor volume (mm3)
900
800
700
600
500
400
300
200
100
0
0
12
26
Days
Cetuximab-(-S-dianthin)1,6 (i.p.)
Cetuximab-(-L-SO1861)3,9(-S-dianthin)2 (i.p.)

Figure 1-4


B
EGFR targeted tumor reduction in A431 tumors of tumor bearing mice
1000,00
800,00
600,00
400,00
200,00
0,00
Tumor volume (mm3)
12 14 17 20 23 26 29 32 35
Days
Cetuximab-(-L-dianthin)1,6 (i.p.)
Cetuximab-(-L-SO1861)3,9 (-L-dianthin)2 (i.p.)

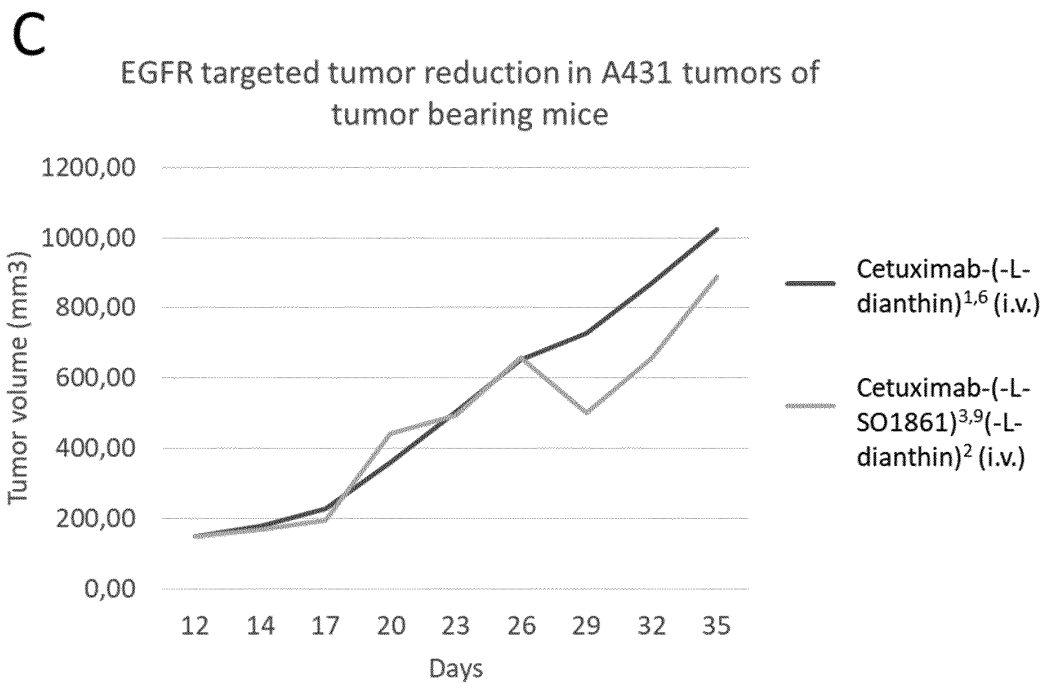

C
EGFR targeted tumor reduction in A431 tumors of tumor bearing mice
1200,00
1000,00
800,00
600,00
400,00
200,00
0,00
Tumor volume (mm3)
12 14 17 20 23 26 29 32 35
Days
Cetuximab-(-L-dianthin)1,6 (i.v.)
Cetuximab-(-L-SO1861)3,9(-L-dianthin)2 (i.v.)

Figure 2-4

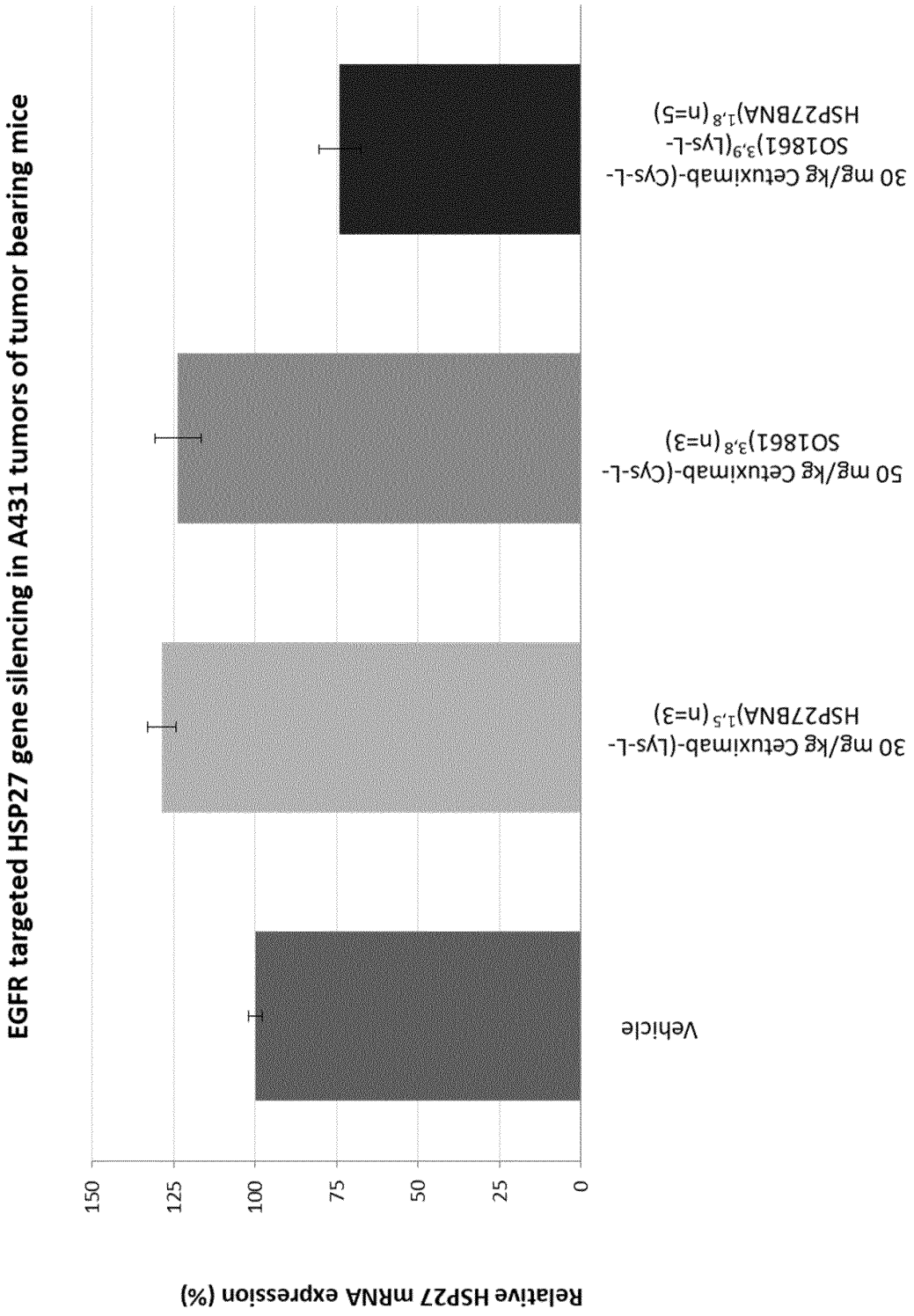

EGFR targeted HSP27 gene silencing in A431 tumors of tumor bearing mice
Relative HSP27 mRNA expression (%)
150
125
100
75
50
25
0
Vehicle
30 mg/kg Cetuximab-(Lys-L-HSP27BNA)1,5 (n=3)
50 mg/kg Cetuximab-(Cys-L-SO1861)3,8 (n=3)
30 mg/kg Cetuximab-(Cys-L-SO1861)3,9(Lys-L-HSP27BNA)1,8 (n=5)

Figure 3-4

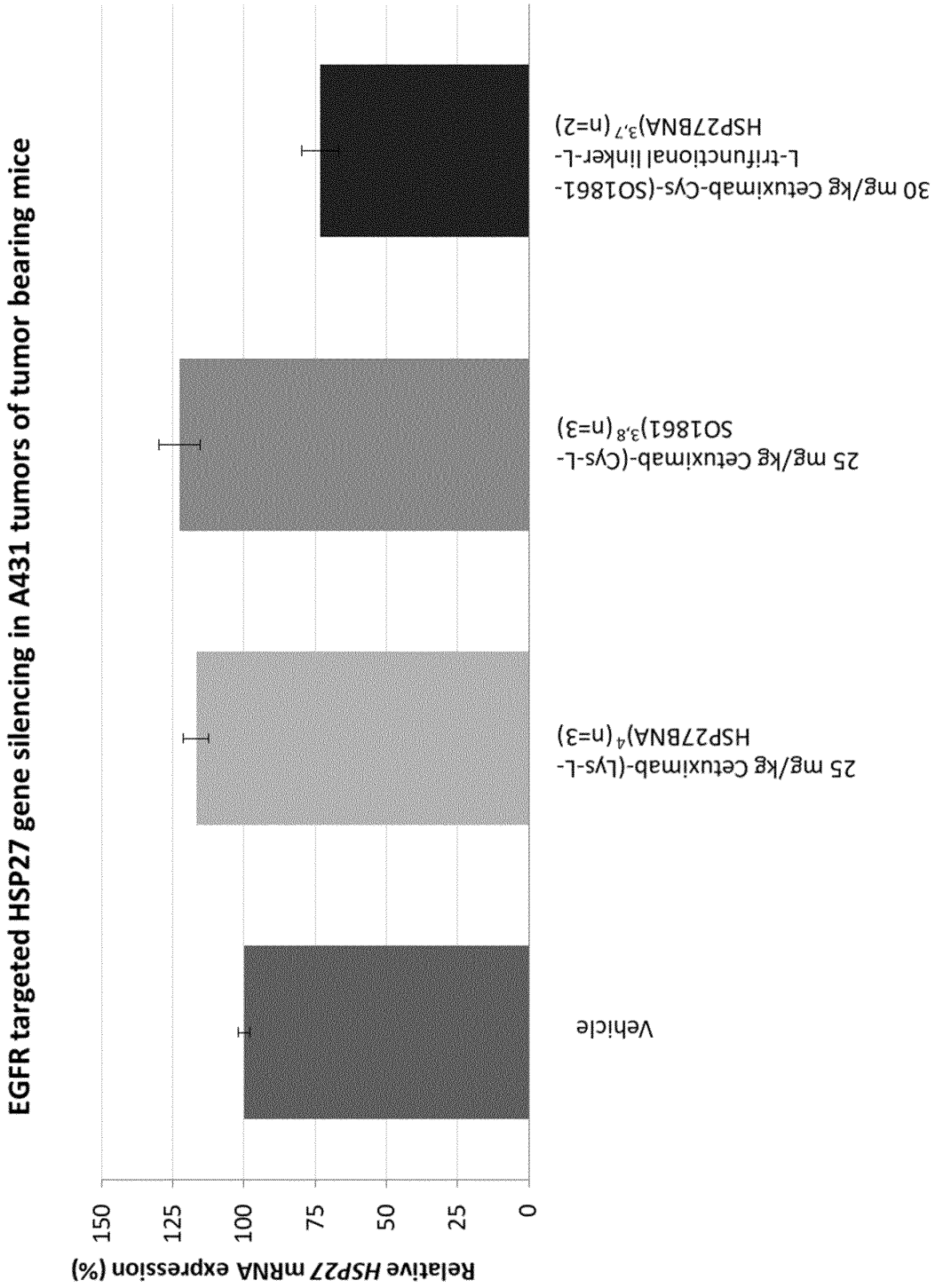

EGFR targeted HSP27 gene silencing in A431 tumors of tumor bearing mice
Relative HSP27 mRNA expression (%)
150
125
100
75
50
25
0
Vehicle
25 mg/kg Cetuximab-(Lys-L-HSP27BNA)4 (n=3)
25 mg/kg Cetuximab-(Cys-L-SO1861)3,8 (n=3)
30 mg/kg Cetuximab-Cys-(SO1861-L-trifunctional linker-L-HSP27BNA)3,7 (n=2)

Figure 4-4

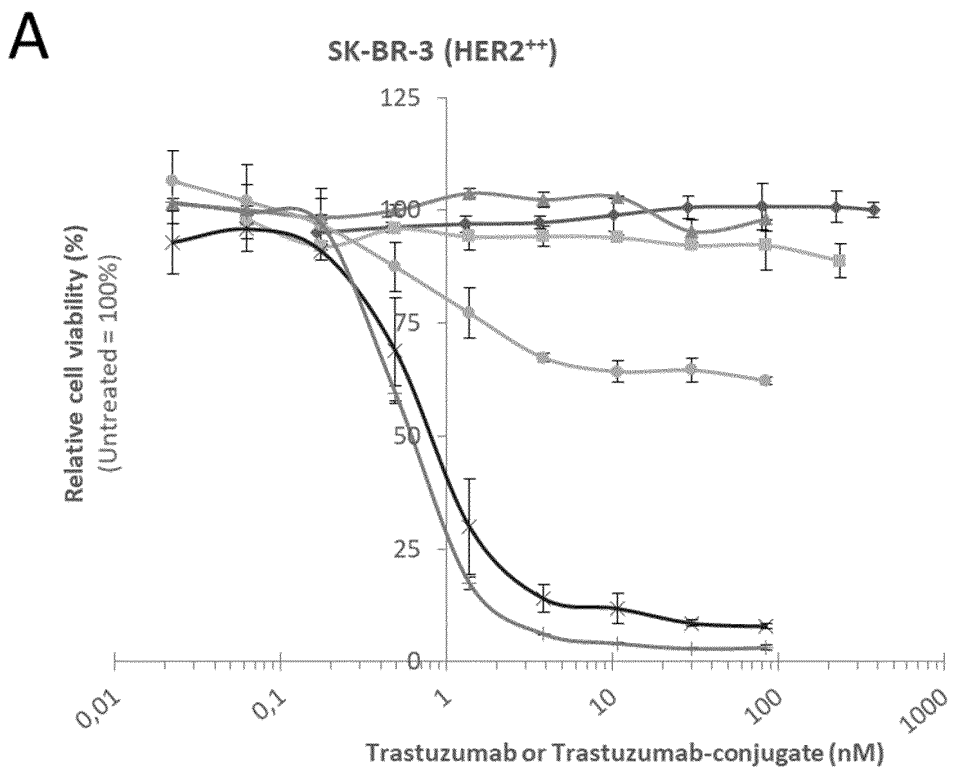

A
SK-BR-3 (HER2++)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,01
0,1
1
10
100
1000
Trastuzumab or Trastuzumab-conjugate (nM)

Figure 4-4

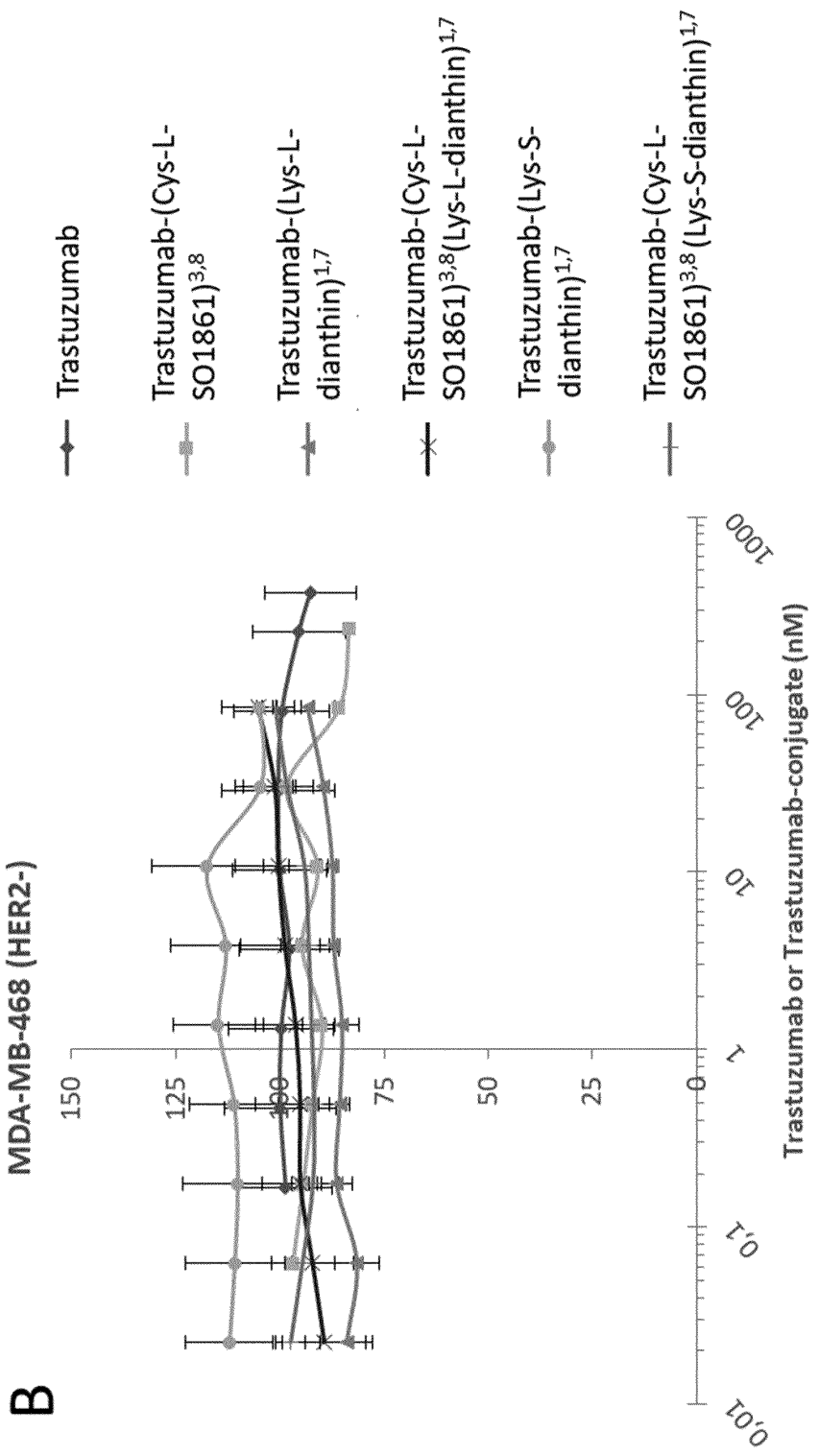
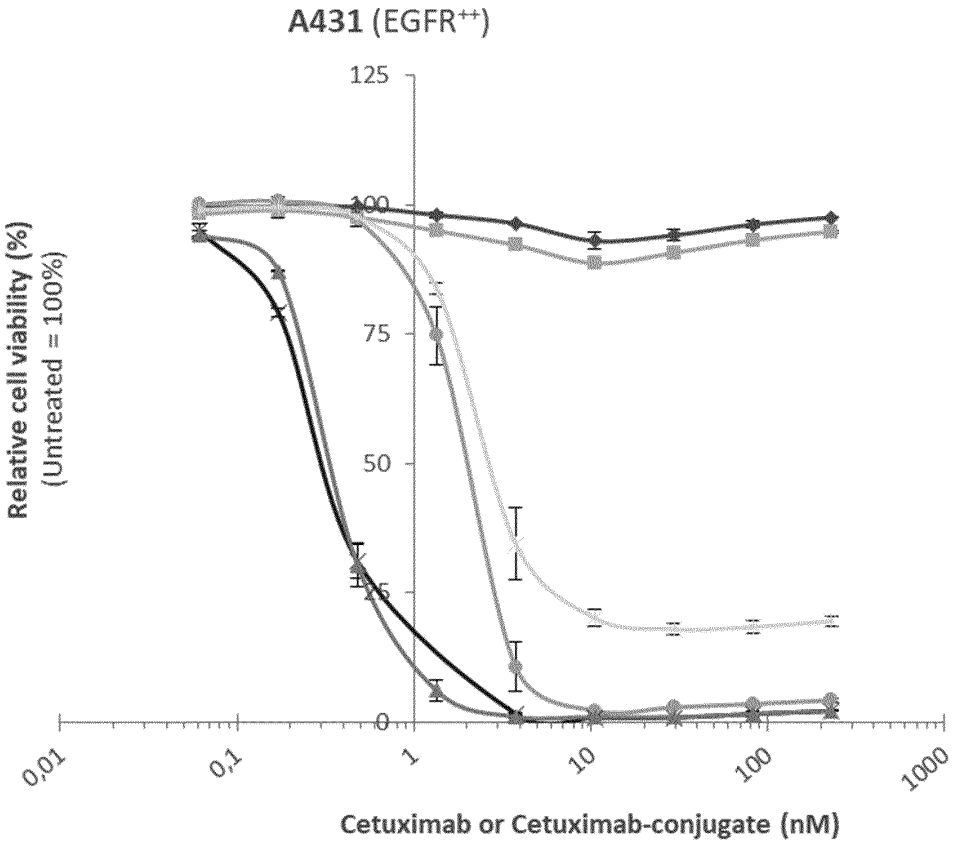

B
MDA-MB-468 (HER2-)
Trastuzumab
Trastuzumab-(Cys-L-SO1861)3,8
Trastuzumab-(Lys-L-dianthin)1,7
Trastuzumab-(Cys-L-SO1861)3,8(Lys-L-dianthin)1,7
Trastuzumab-(Lys-S-dianthin)1,7
Trastuzumab-(Cys-L-SO1861)3,8(Lys-S-dianthin)1,7
150
125
100
75
50
25
0
0,01
0,1
1
10
100
1000
Trastuzumab or Trastuzumab-conjugate (nM)

Figure 4-4

C


A431 (EGFR++)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,01
0,1
1
10
100
1000
Cetuximab or Cetuximab-conjugate (nM)

D

Figure 4-4

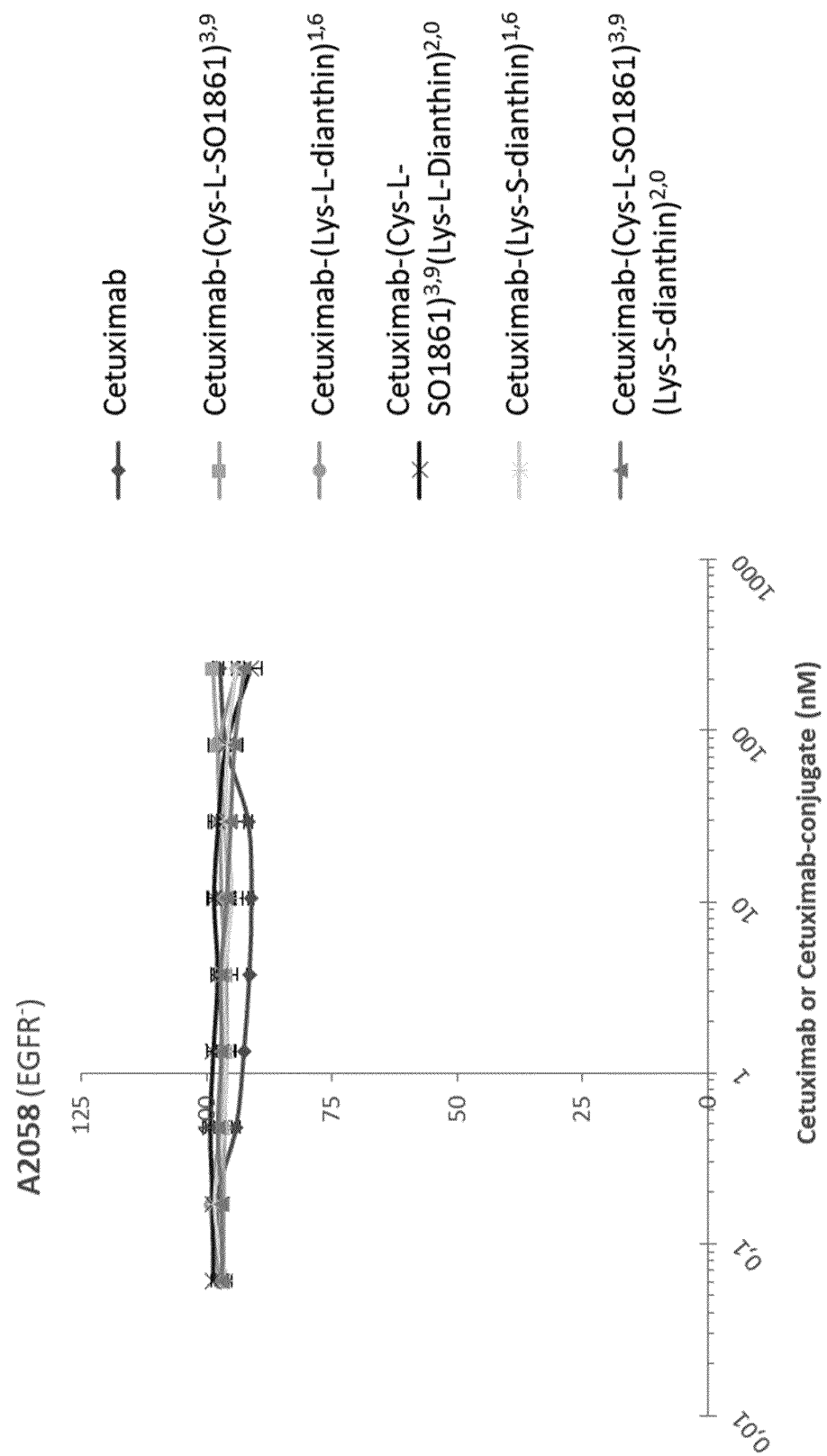

A2058 (EGFR-)
125
100
75
50
25
0
0,01
0,1
1
10
100
1000
Cetuximab or Cetuximab-conjugate (nM)
Cetuximab
Cetuximab-(Cys-L-SO1861)3,9
Cetuximab-(Lys-L-dianthin)1,6
Cetuximab-(Cys-L-SO1861)3,9(Lys-L-Dianthin)2,0
Cetuximab-(Lys-S-dianthin)1,6
Cetuximab-(Cys-L-SO1861)3,9(Lys-S-dianthin)2,0

Figure 5-4

A

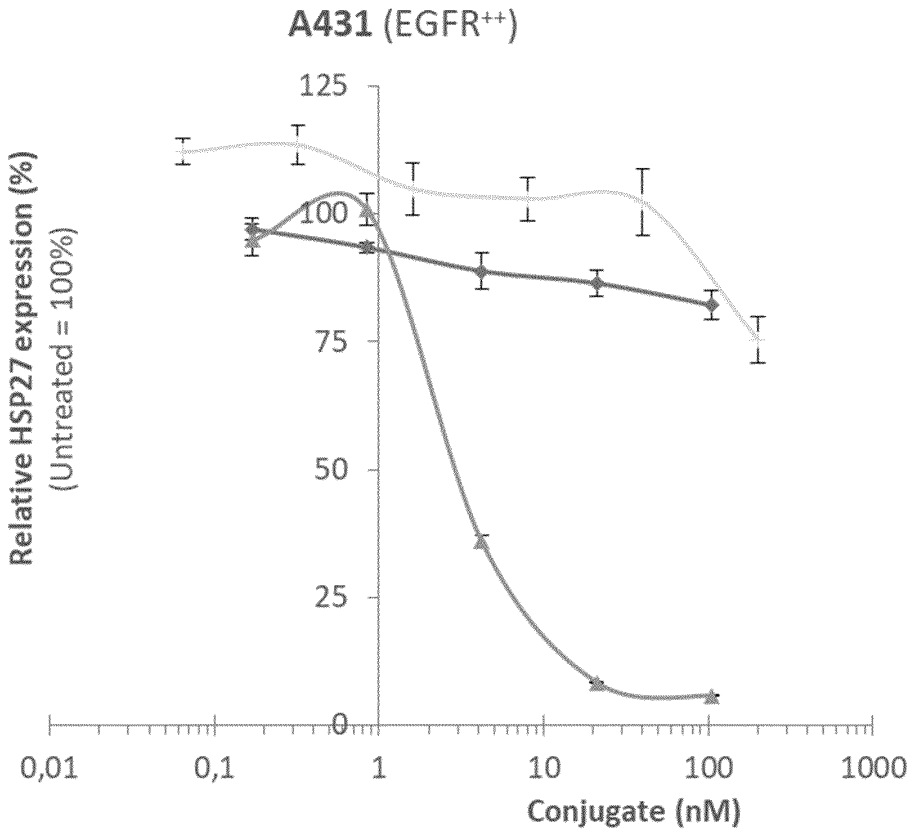

A431 (EGFR++)
Relative HSP27 expression (%)
(Untreated = 100%)
125
100
75
50
25
0
0,01
0,1
1
10
100
1000
Conjugate (nM)

Figure 5-4

B

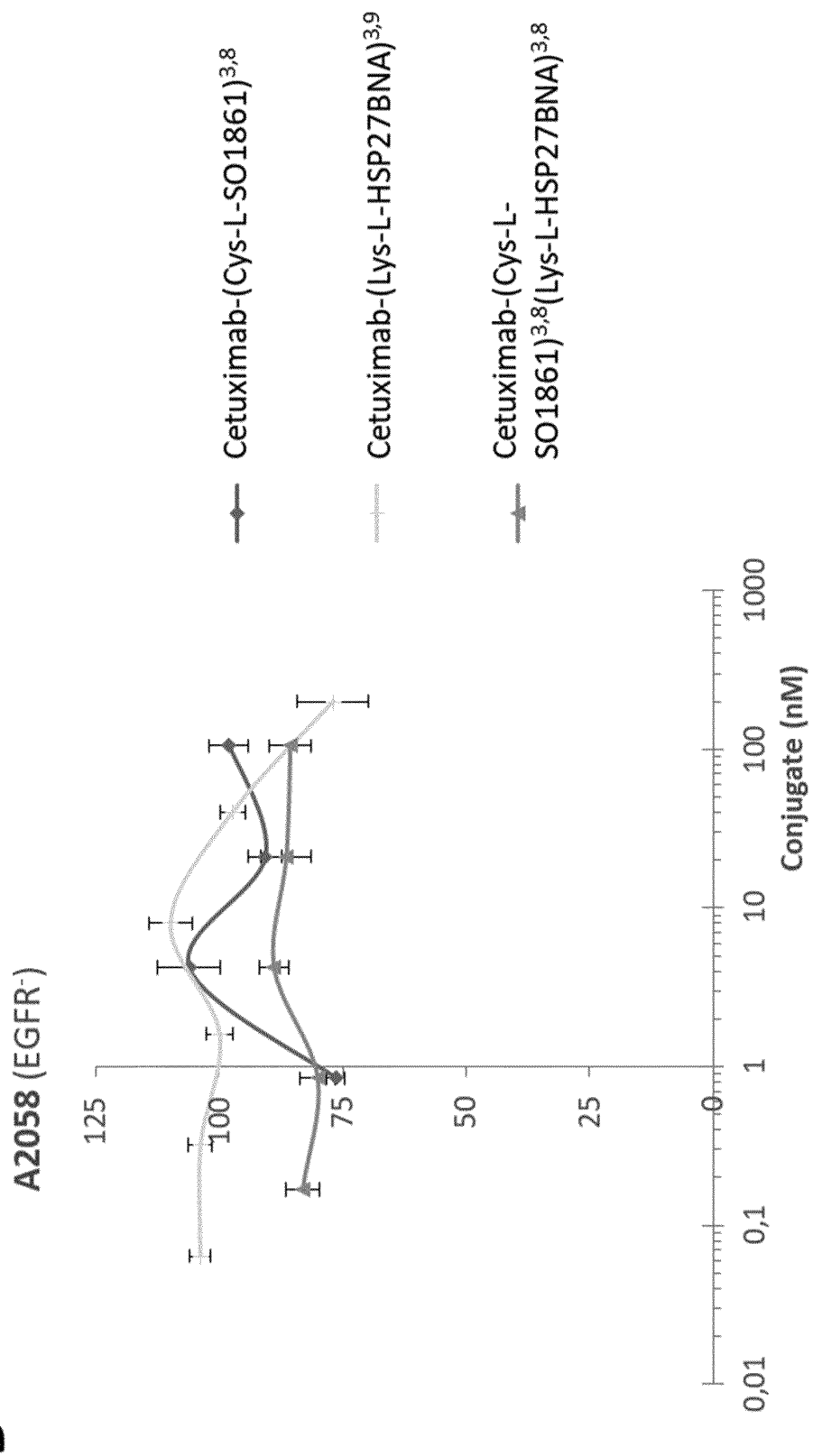

A2058 (EGFR-)
125
100
75
50
25
0
0,01
0,1
1
10
100
1000
Conjugate (nM)
Cetuximab-(Cys-L-SO1861)3,8
Cetuximab-(Lys-L-HSP27BNA)3,9
Cetuximab-(Cys-L-SO1861)3,8(Lys-L-HSP27BNA)3,8

Figure 6-4

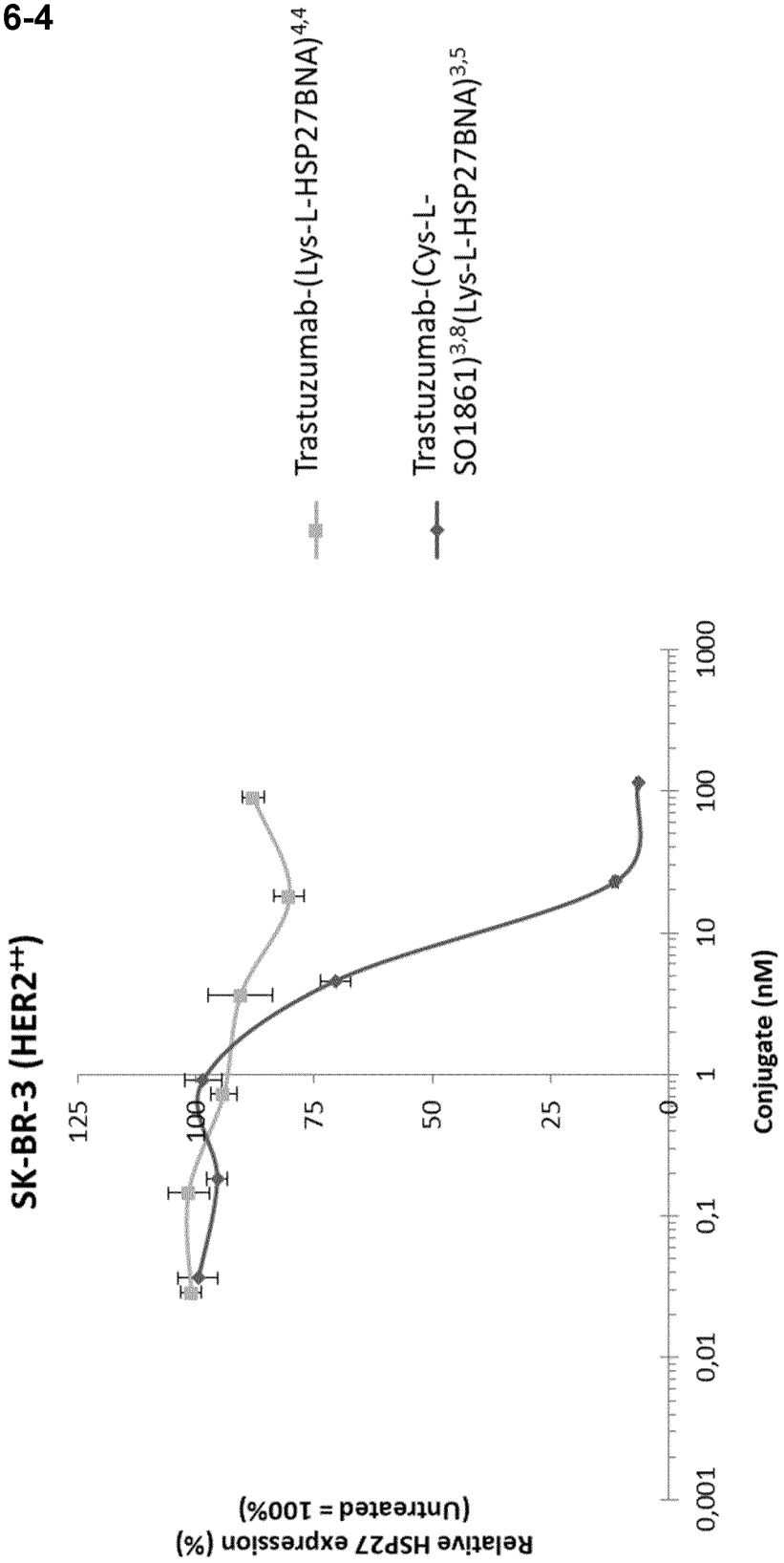
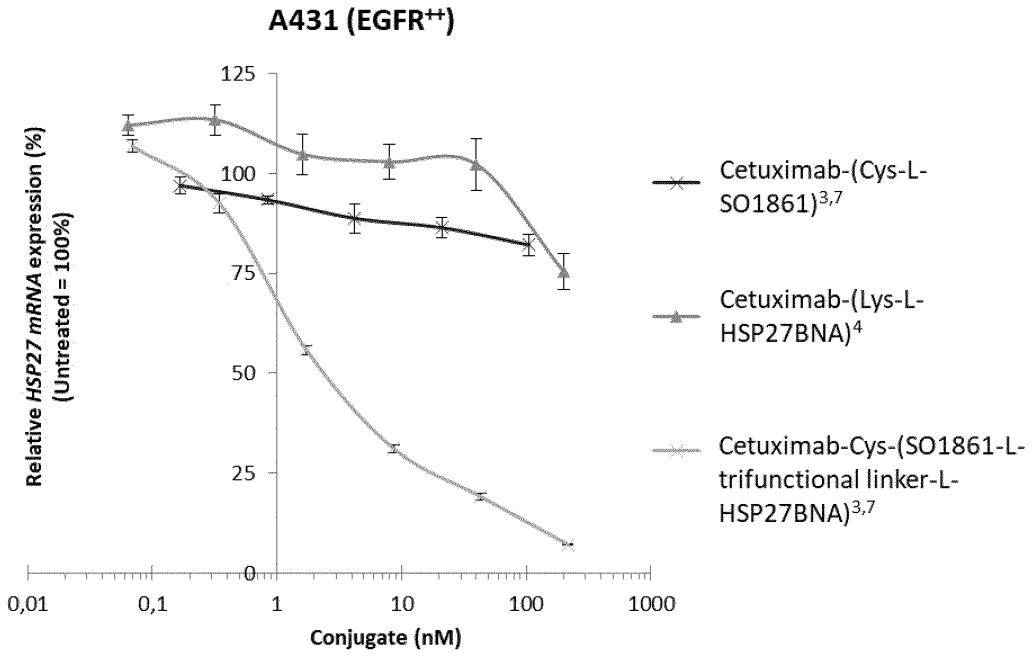

Trastuzumab-(Lys-L-HSP27BNA)4,4
Trastuzumab-(Cys-L-SO1861)3,8(Lys-L-HSP27BNA)3,5
SK-BR-3 (HER2++)
Relative HSP27 expression (%)
(Untreated = 100%)
125
100
75
50
25
0
0,001
0,01
0,1
1
10
100
1000
Conjugate (nM)

Figure 7-4

A


A431 (EGFR++)
Relative HSP27 mRNA expression (%)
(Untreated = 100%)
125
100
75
50
25
0
0,01
0,1
1
10
100
1000
Conjugate (nM)
Cetuximab-(Cys-L-SO1861)3,7
Cetuximab-(Lys-L-HSP27BNA)4
Cetuximab-Cys-(SO1861-L-trifunctional linker-L-HSP27BNA)3,7

B

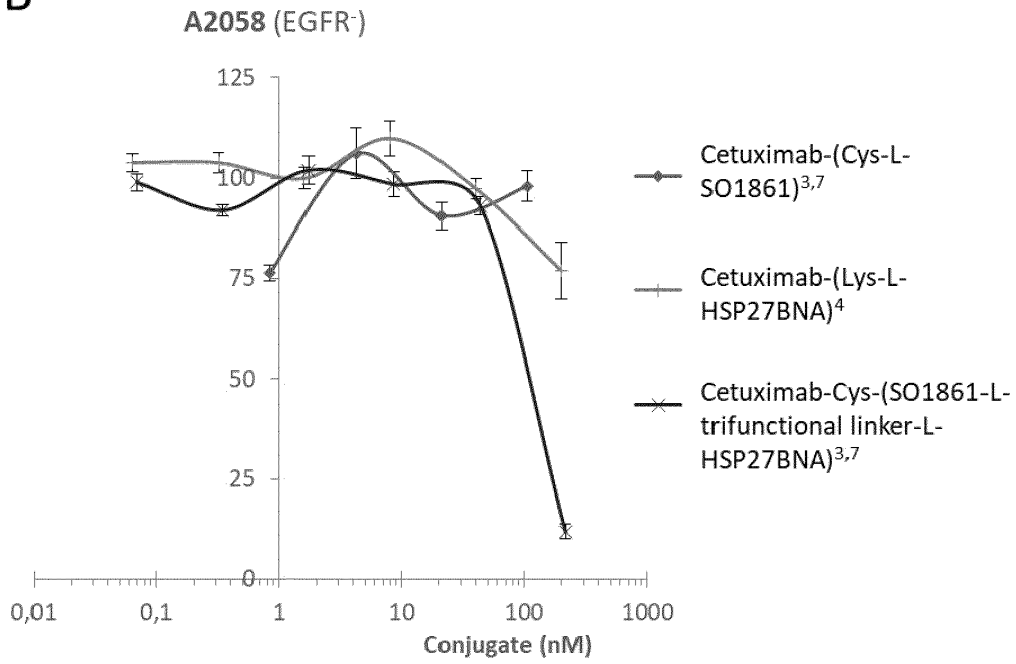
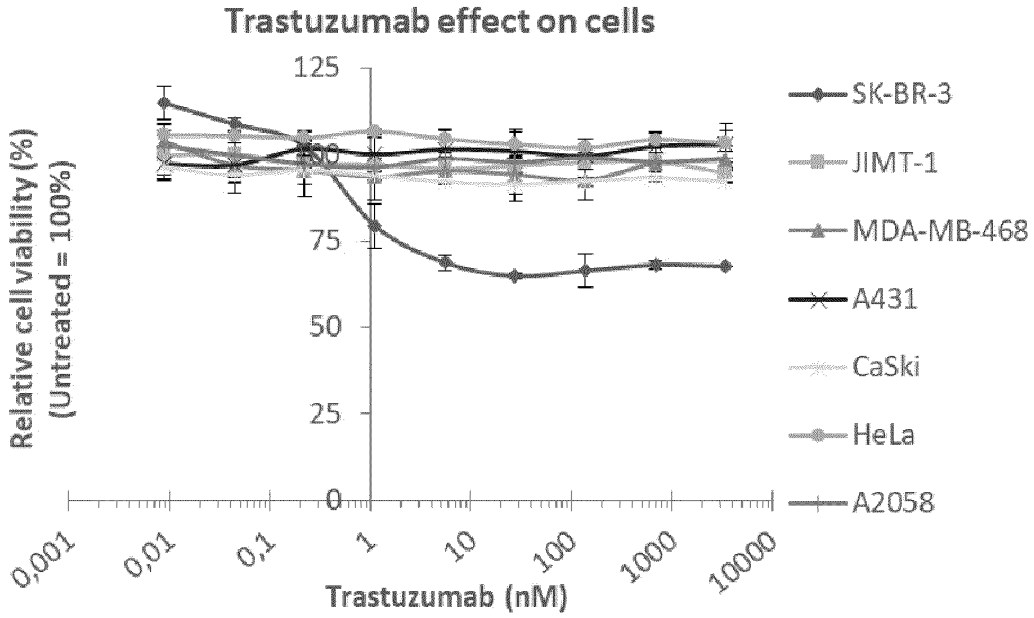

A2058 (EGFR-)
125
100
75
50
25
0
0,01
0,1
1
10
100
1000
Conjugate (nM)
Cetuximab-(Cys-L-SO1861)3,7
Cetuximab-(Lys-L-HSP27BNA)4
Cetuximab-Cys-(SO1861-L-trifunctional linker-L-HSP27BNA)3,7

Figure 8-4

A


Trastuzumab effect on cells
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,001
0,01
0,1
1
10
100
1000
10000
Trastuzumab (nM)
SK-BR-3
JIMT-1
MDA-MB-468
A431
CaSki
HeLa
A2058

B

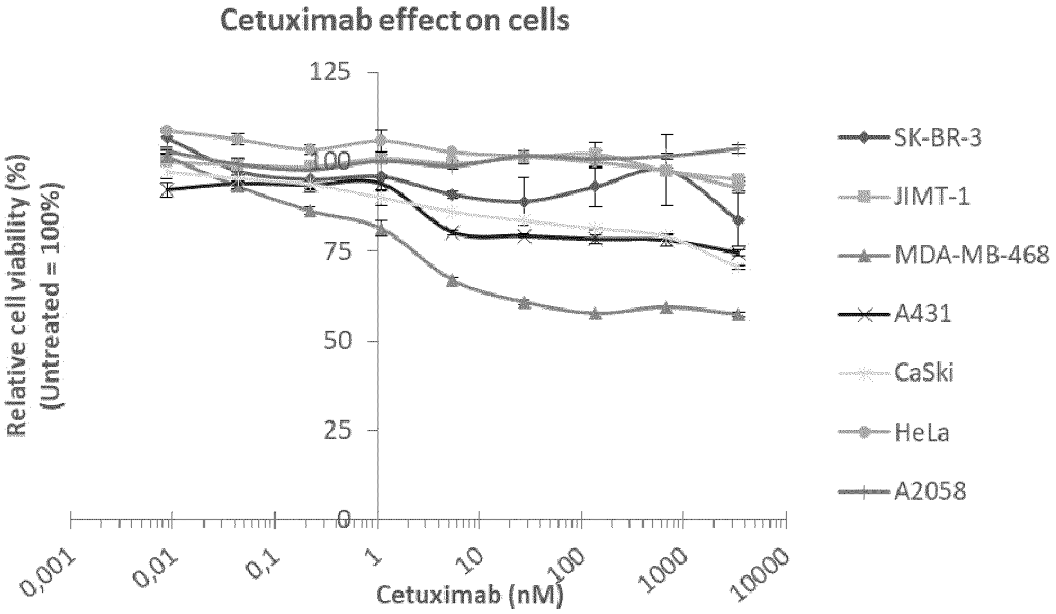
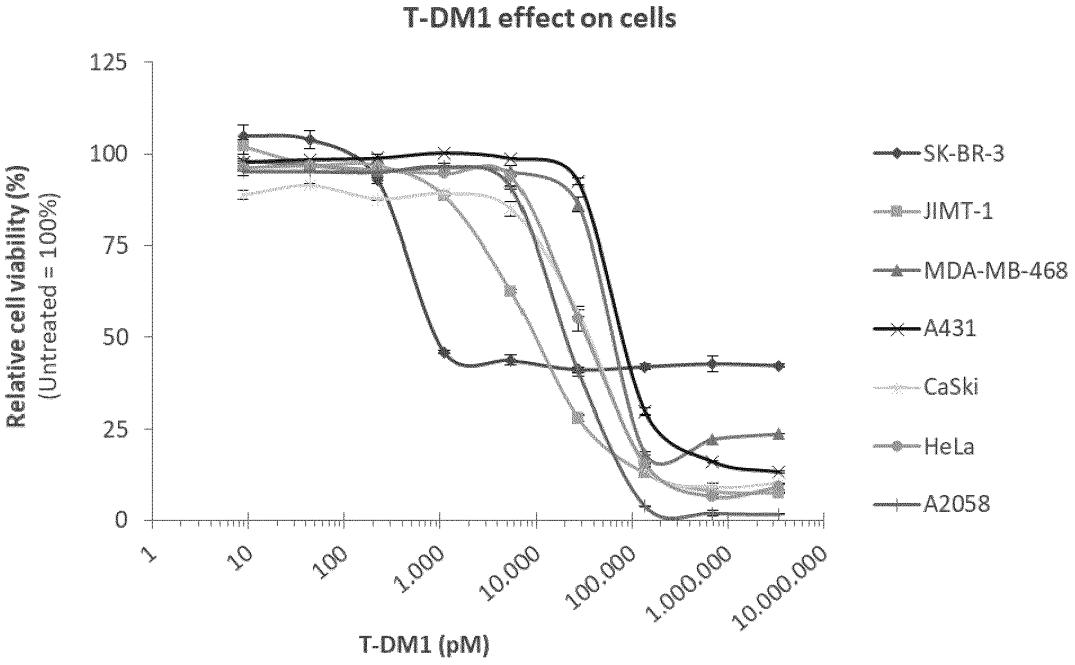

Cetuximab effect on cells
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,001
0,01
0,1
1
10
100
1000
10000
Cetuximab (nM)
SK-BR-3
JIMT-1
MDA-MB-468
A431
CaSki
HeLa
A2058

Figure 8-4

C


T-DM1 effect on cells
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
1
10
100
1.000
10.000
100.000
1.000.000
10.000.000
T-DM1 (pM)
SK-BR-3
JIMT-1
MDA-MB-468
A431
CaSki
HeLa
A2058

D

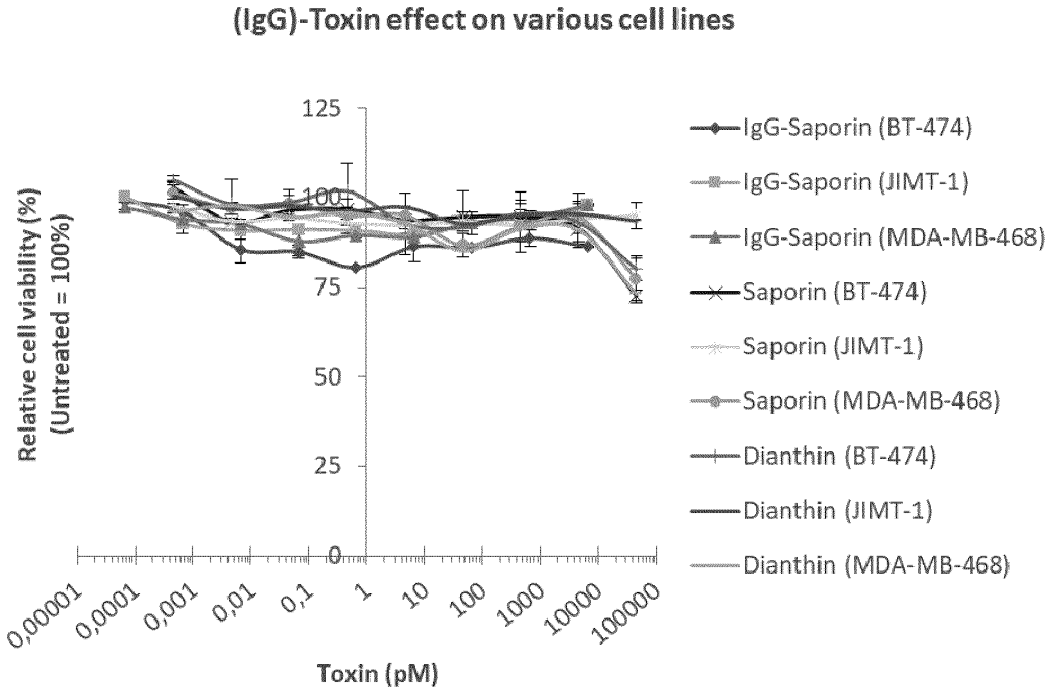

(IgG)-Toxin effect on various cell lines
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,00001
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
100000
Toxin (pM)
IgG-Saporin (BT-474)
IgG-Saporin (JIMT-1)
IgG-Saporin (MDA-MB-468)
Saporin (BT-474)
Saporin (JIMT-1)
Saporin (MDA-MB-468)
Dianthin (BT-474)
Dianthin (JIMT-1)
Dianthin (MDA-MB-468)

Figure 9-4

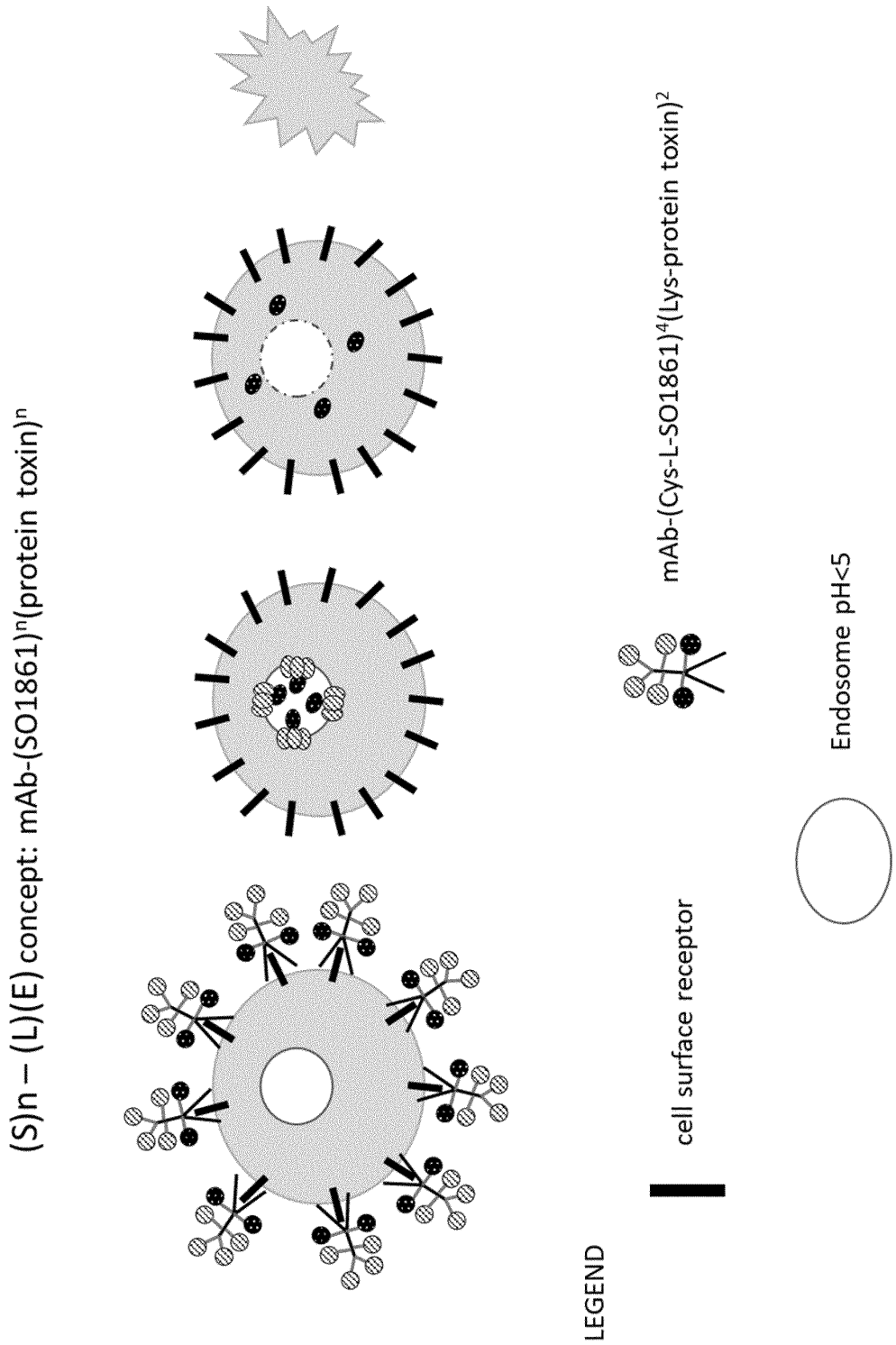

(S)n – (L)(E) concept: mAb-(SO1861)n(protein toxin)n
LEGEND
cell surface receptor
mAb-(Cys-L-SO1861)4(Lys-protein toxin)2
Endosome pH<5

Figure 10-4

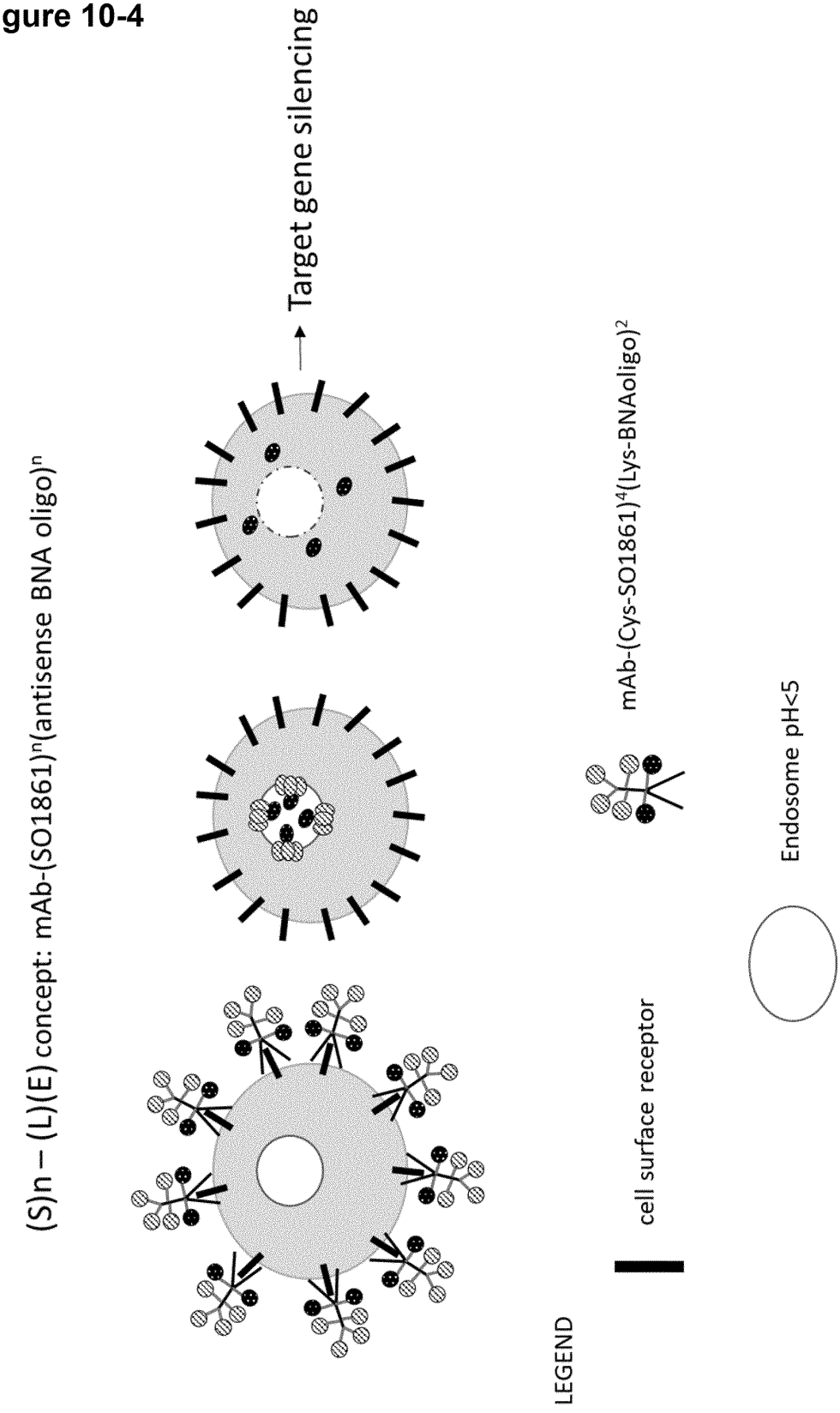

(S)n – (L)(E) concept: mAb-(SO1861)n(antisense BNA oligo)n
Target gene silencing
mAb-(Cys-SO1861)4(Lys-BNAoligo)2
LEGEND
cell surface receptor
Endosome pH<5

Figure 11-4

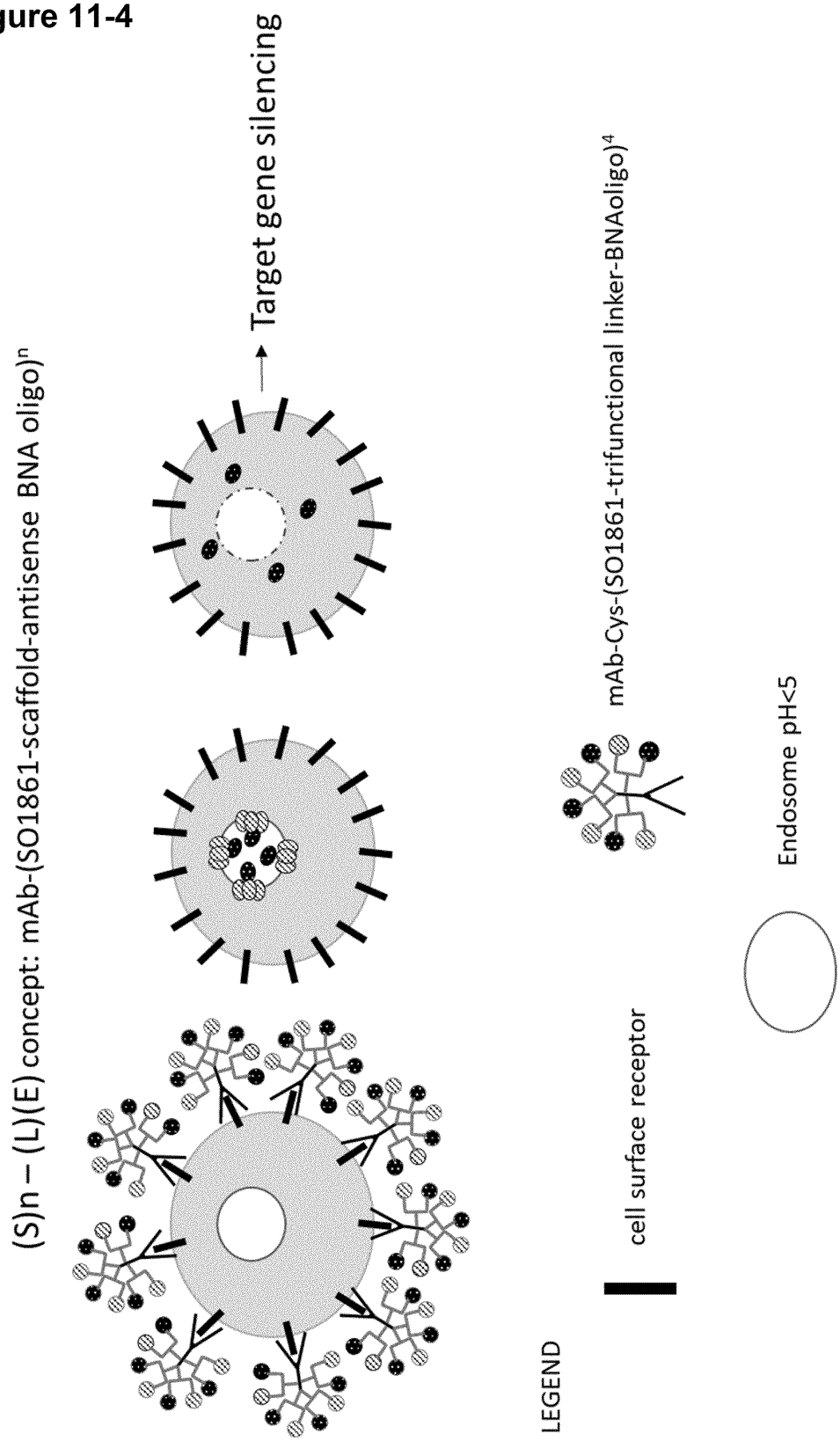

(S)n – (L)(E) concept: mAb-(SO1861-scaffold-antisense BNA oligo)n
Target gene silencing
mAb-Cys-(SO1861-trifunctional linker-BNAoligo)4
LEGEND
cell surface receptor
Endosome pH<5

Figure 12-4

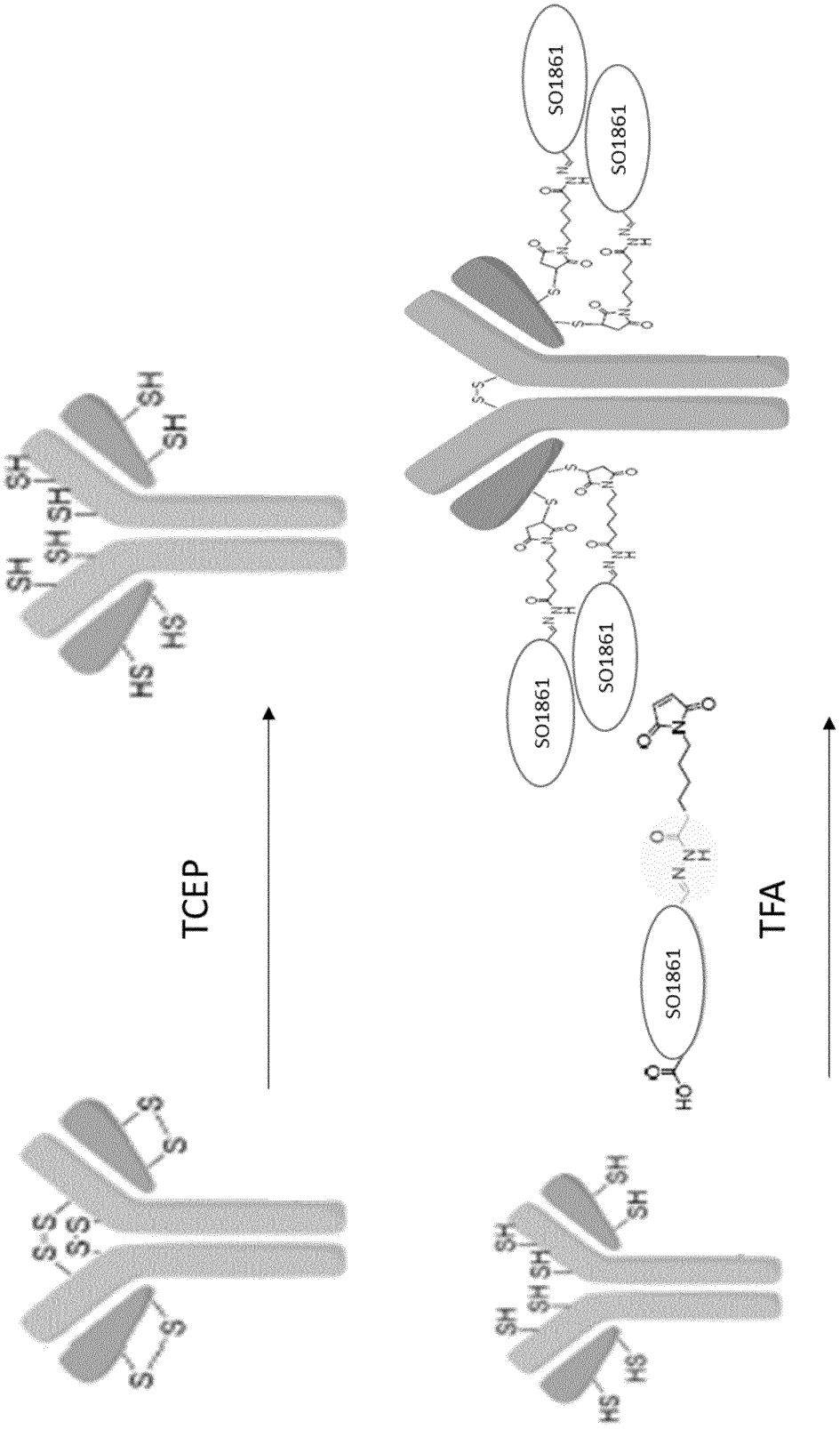


Figure 1-5

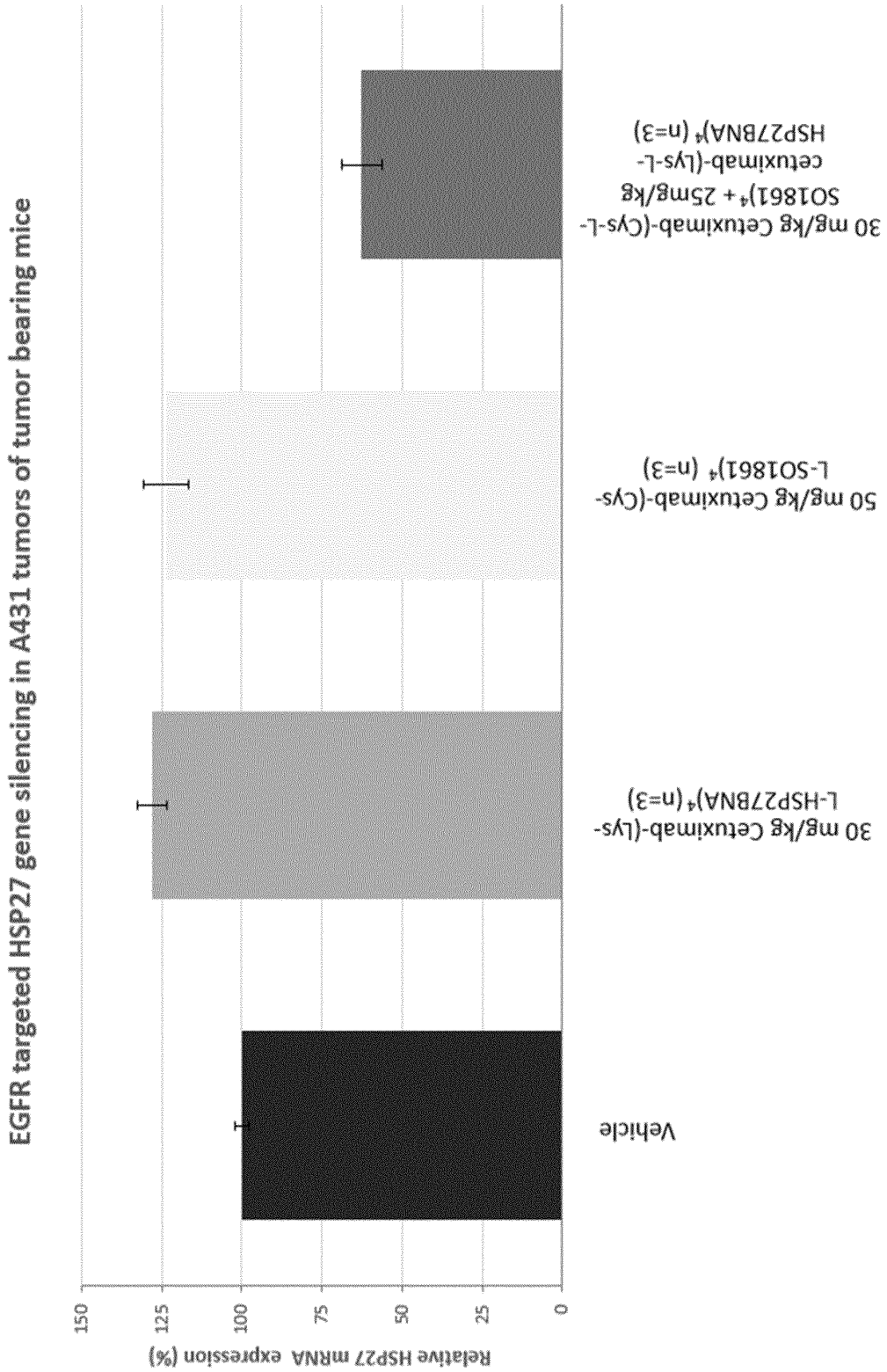

EGFR targeted HSP27 gene silencing in A431 tumors of tumor bearing mice
Relative HSP27 mRNA expression (%)
150
125
100
75
50
25
0
Vehicle
30 mg/kg Cetuximab-(Lys-L-HSP27BNA)4 (n=3)
50 mg/kg Cetuximab-(Cys-L-SO1861)4 (n=3)
30 mg/kg Cetuximab-(Cys-L-SO1861)4 + 25mg/kg cetuximab-(Lys-L-HSP27BNA)4 (n=3)

Figure 2-5

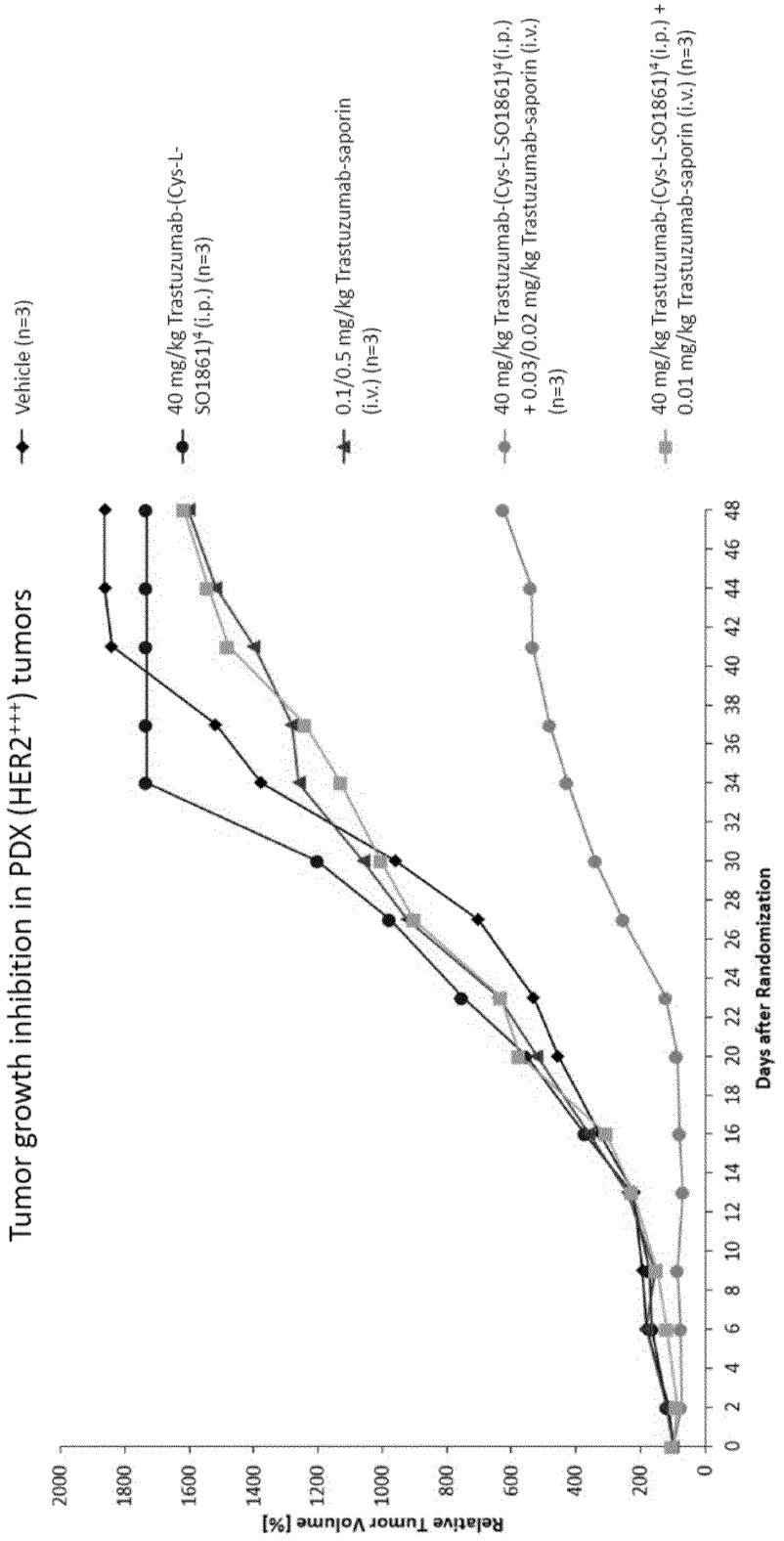

Tumor growth inhibition in PDX (HER2+++) tumors
Vehicle (n=3)
40 mg/kg Trastuzumab-(Cys-L-SO1861)4 (i.p.) (n=3)
0.1/0.5 mg/kg Trastuzumab-saporin (i.v.) (n=3)
40 mg/kg Trastuzumab-(Cys-L-SO1861)4 (i.p.) + 0.03/0.02 mg/kg Trastuzumab-saporin (i.v.) (n=3)
40 mg/kg Trastuzumab-(Cys-L-SO1861)4 (i.p.) + 0.01 mg/kg Trastuzumab-saporin (i.v.) (n=3)
Relative Tumor Volume [%]
Days after Randomization

Figure 3-5

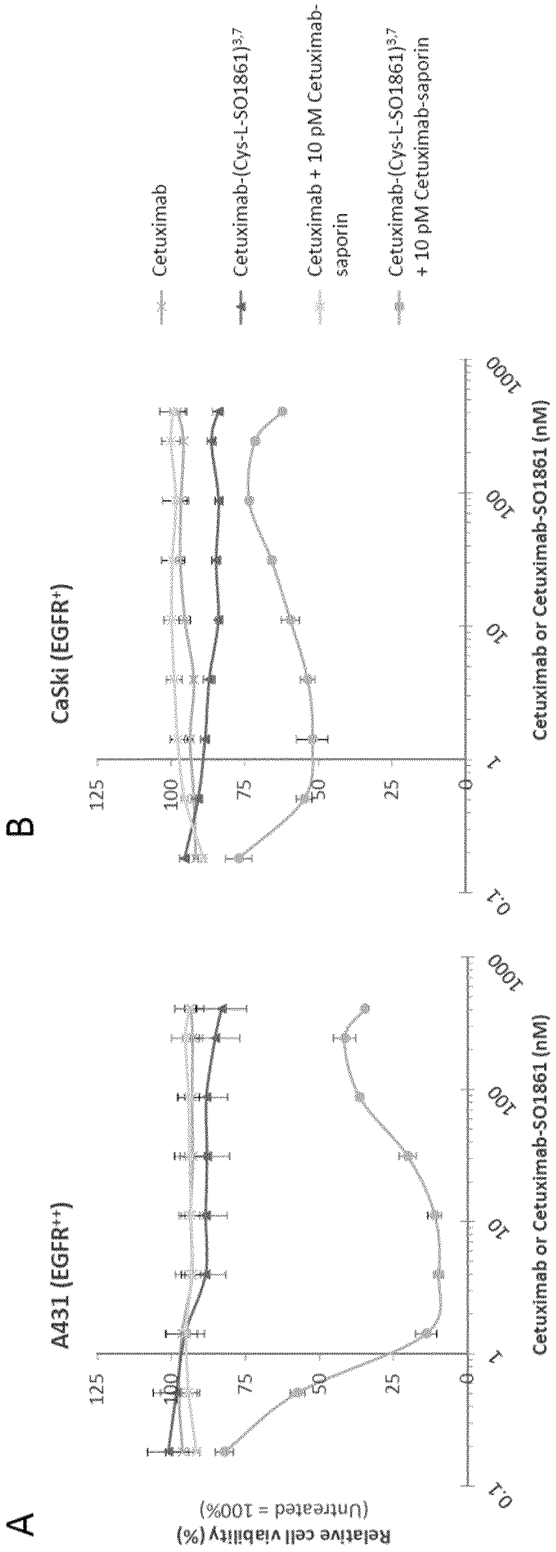

A
B
A431 (EGFR++)
CaSki (EGFR+)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0.1
1
10
100
1000
Cetuximab or Cetuximab-SO1861 (nM)
Cetuximab
Cetuximab-(Cys-L-SO1861)3.7
Cetuximab + 10 pM Cetuximab-saporin
Cetuximab-(Cys-L-SO1861)3.7 + 10 pM Cetuximab-saporin

Figure 3-5

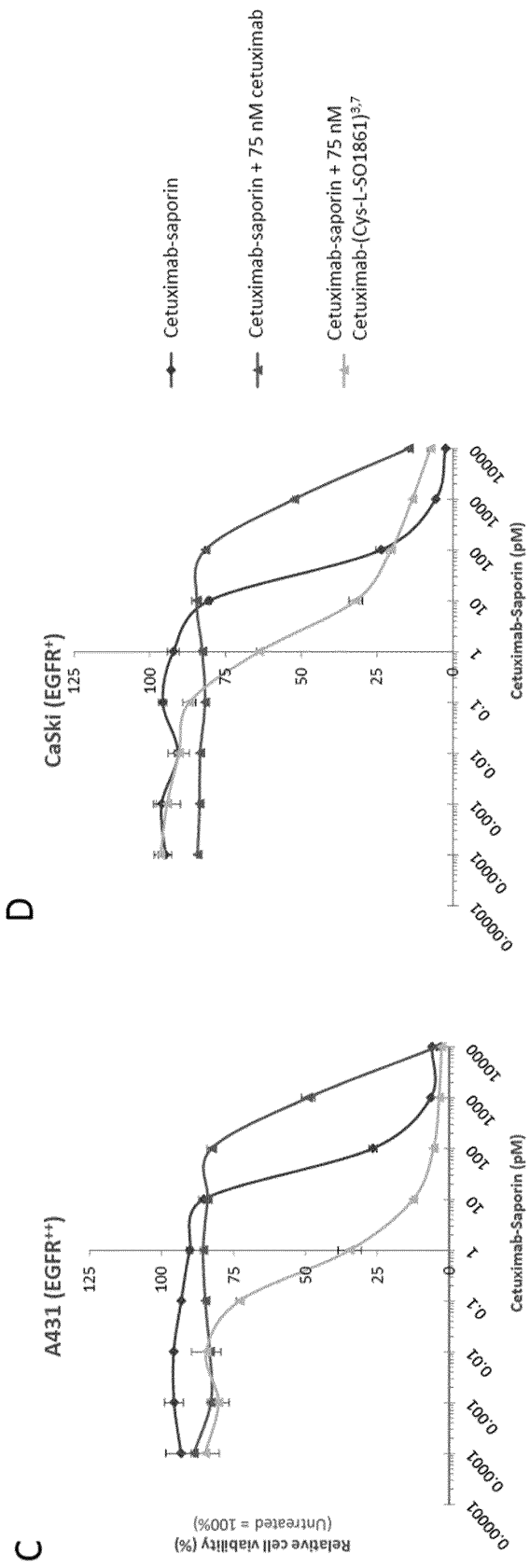

Cetuximab-saporin
Cetuximab-saporin + 75 nM cetuximab
Cetuximab-saporin + 75 nM Cetuximab-(Cys-L-SO1861)3,7
D
CaSki (EGFR++)
125
100
75
50
25
0
Cetuximab-Saporin (pM)
10000
1000
100
10
1
0,1
0,01
0,001
0,0001
0,00001
C
A431 (EGFR+++)
Relative cell viability (%)
(Untreated = 100%)

Figure 4-5

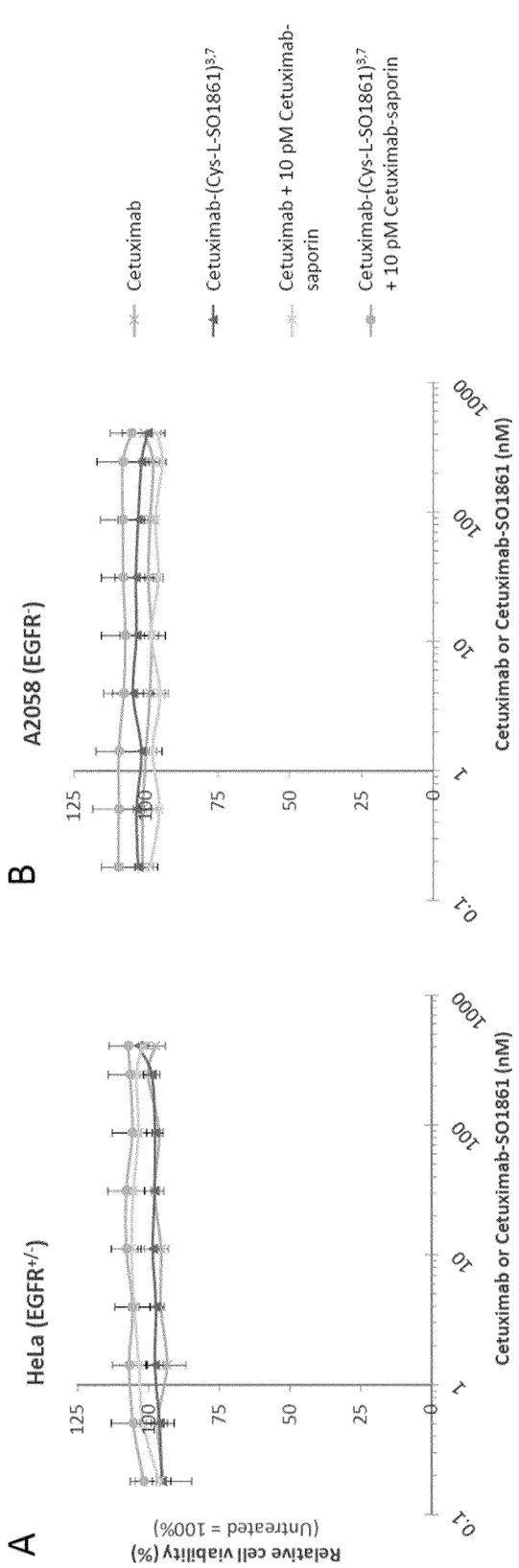

A
HeLa (EGFR+/-)
B
A2058 (EGFR-)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0.1
1
10
100
1000
Cetuximab or Cetuximab-SO1861 (nM)
Cetuximab
Cetuximab-(Cys-L-SO1861)3,7
Cetuximab + 10 pM Cetuximab-saporin
Cetuximab-(Cys-L-SO1861)3,7 + 10 pM Cetuximab-saporin

Figure 4-5

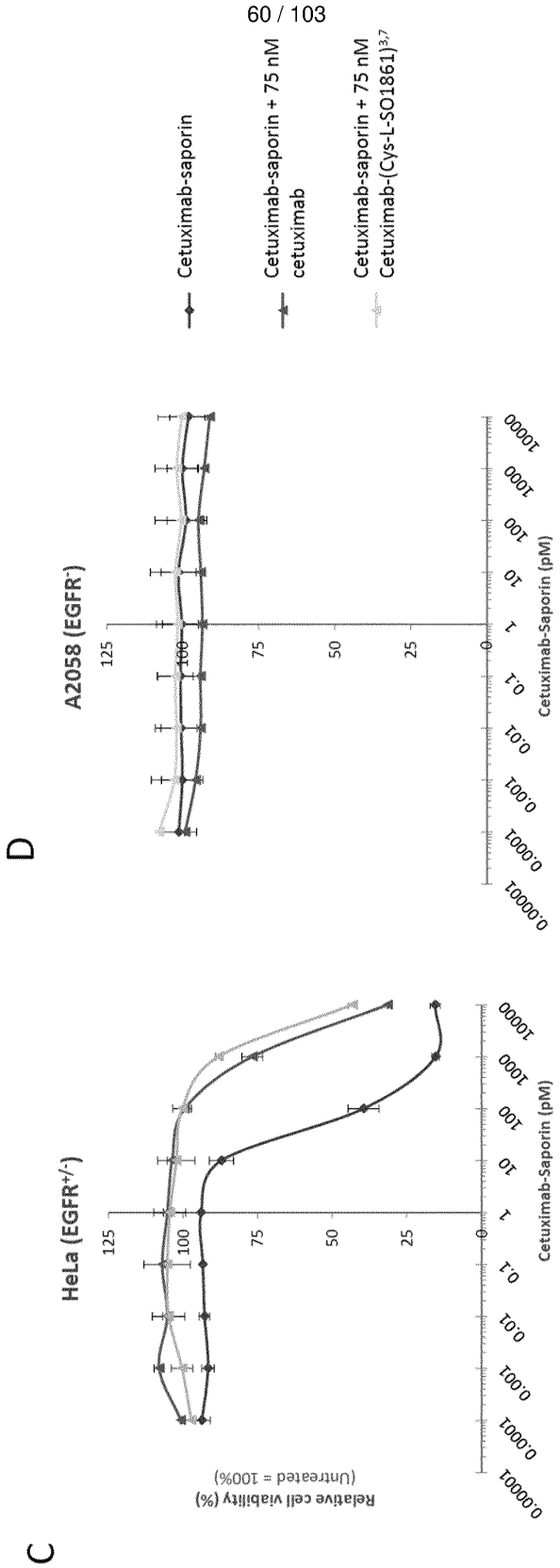

C
HeLa (EGFR+/-)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
Cetuximab-Saporin (pM)
0.0001
0.001
0.01
0.1
1
10
100
1000
10000
D
A2058 (EGFR-)
Cetuximab-saporin
Cetuximab-saporin + 75 nM cetuximab
Cetuximab-saporin + 75 nM Cetuximab-(Cys-L-SO1861)3,7

Figure 5-5

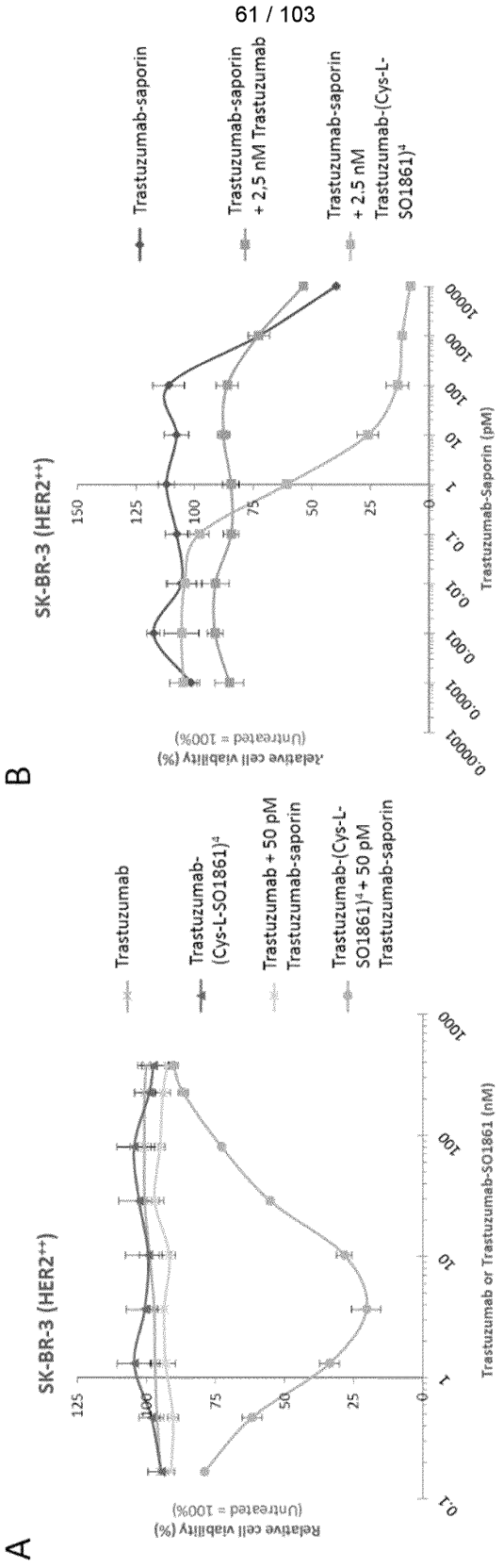

A
SK-BR-3 (HER2++)
Relative cell viability (%)
(Untreated = 100%)
Trastuzumab
Trastuzumab-(Cys-L-SO1861)4
Trastuzumab + 50 pM Trastuzumab-saporin
Trastuzumab-(Cys-L-SO1861)4 + 50 pM Trastuzumab-saporin
Trastuzumab or Trastuzumab-SO1861 (nM)
B
SK-BR-3 (HER2++)
Relative cell viability (%)
(Untreated = 100%)
Trastuzumab-saporin
Trastuzumab-saporin + 2,5 nM Trastuzumab
Trastuzumab-saporin + 2.5 nM Trastuzumab-(Cys-L-SO1861)4
Trastuzumab-Saporin (pM)

Figure 6-5

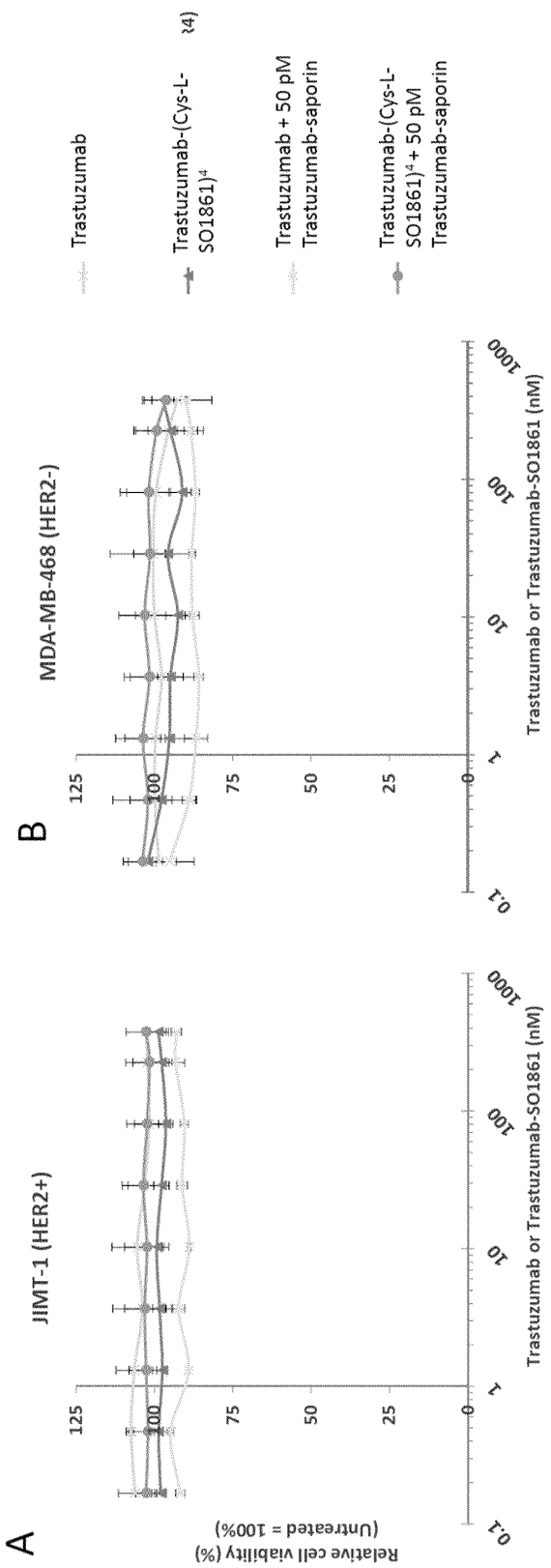

A
JIMT-1 (HER2+)
B
MDA-MB-468 (HER2-)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0.1
1
10
100
1000
Trastuzumab or Trastuzumab-SO1861 (nM)
Trastuzumab
Trastuzumab-(Cys-L-SO1861)4
Trastuzumab + 50 pM Trastuzumab-saporin
Trastuzumab-(Cys-L-SO1861)4 + 50 pM Trastuzumab-saporin

Figure 6-5

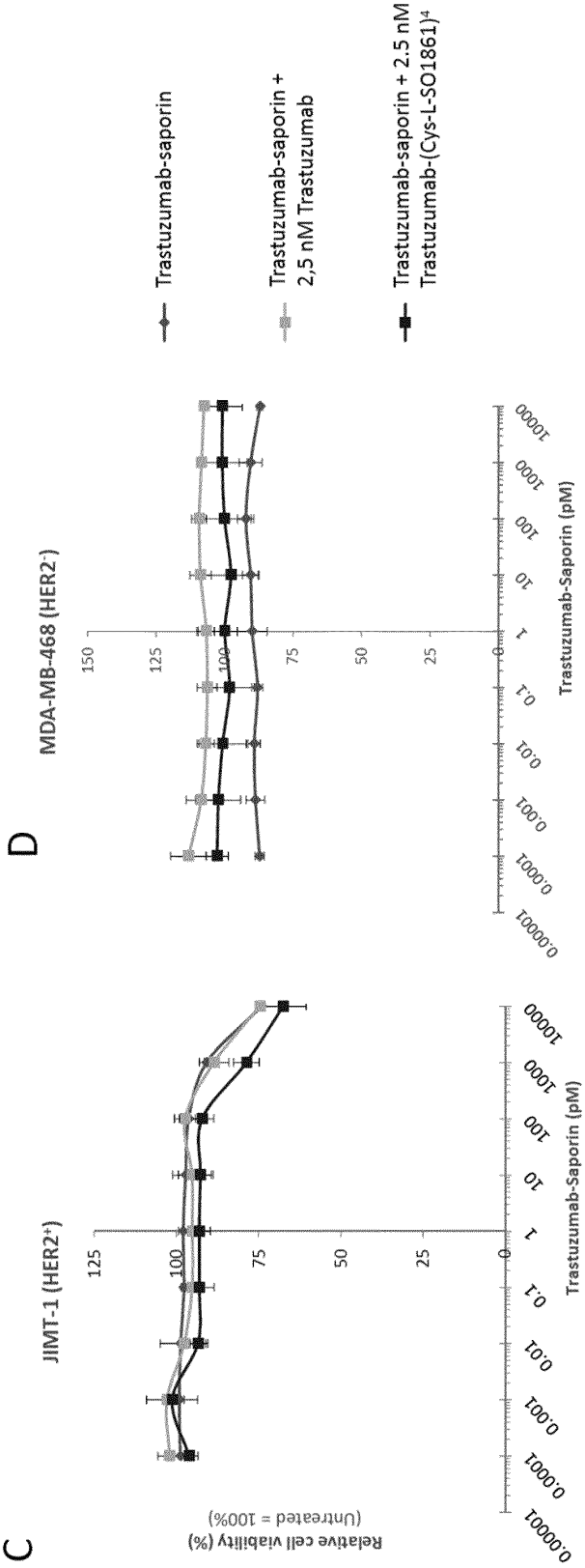

C
JIMT-1 (HER2+)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,00001
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
Trastuzumab-Saporin (pM)
D
MDA-MB-468 (HER2-)
150
125
100
75
50
25
0
0,00001
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
Trastuzumab-Saporin (pM)
Trastuzumab-saporin
Trastuzumab-saporin + 2,5 nM Trastuzumab
Trastuzumab-saporin + 2.5 nM Trastuzumab-(Cys-L-SO1861)4

Figure 7-5

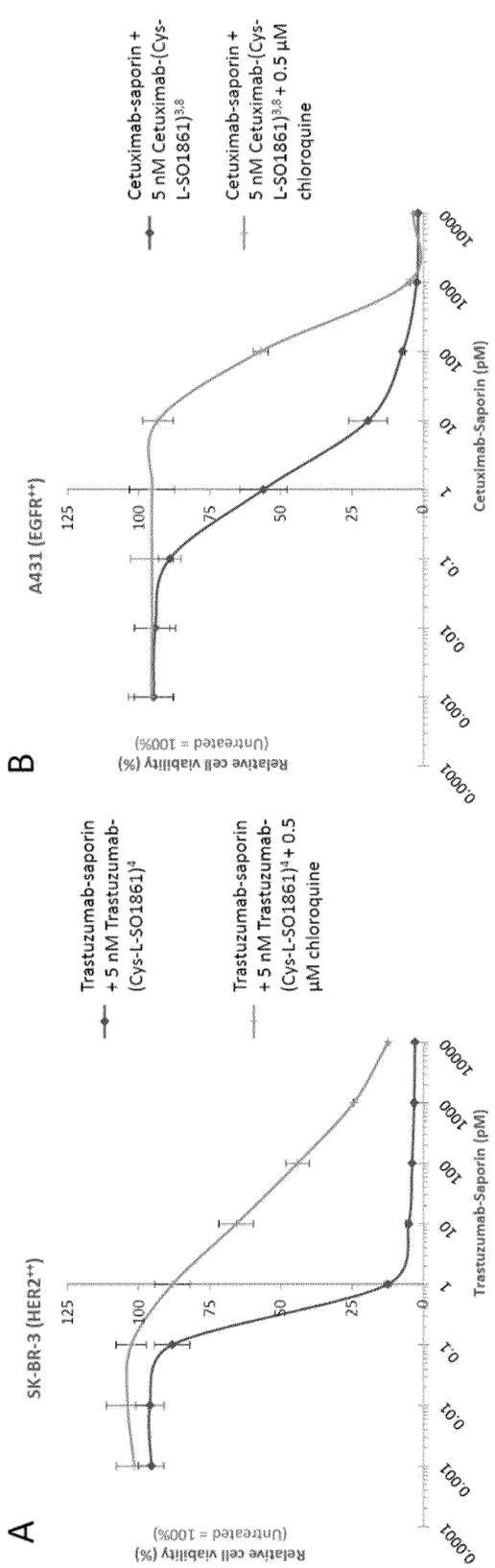

A
SK-BR-3 (HER2++)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
Trastuzumab-Saporin (pM)
Trastuzumab-saporin + 5 nM Trastuzumab-(Cys-L-SO1861)4
Trastuzumab-saporin + 5 nM Trastuzumab-(Cys-L-SO1861)4 + 0.5 µM chloroquine
B
A431 (EGFR++)
Relative cell viability (%)
(Untreated = 100%)
Cetuximab-Saporin (pM)
Cetuximab-saporin + 5 nM Cetuximab-(Cys-L-SO1861)3,8
Cetuximab-saporin + 5 nM Cetuximab-(Cys-L-SO1861)3,8 + 0.5 µM chloroquine

Figure 8-5

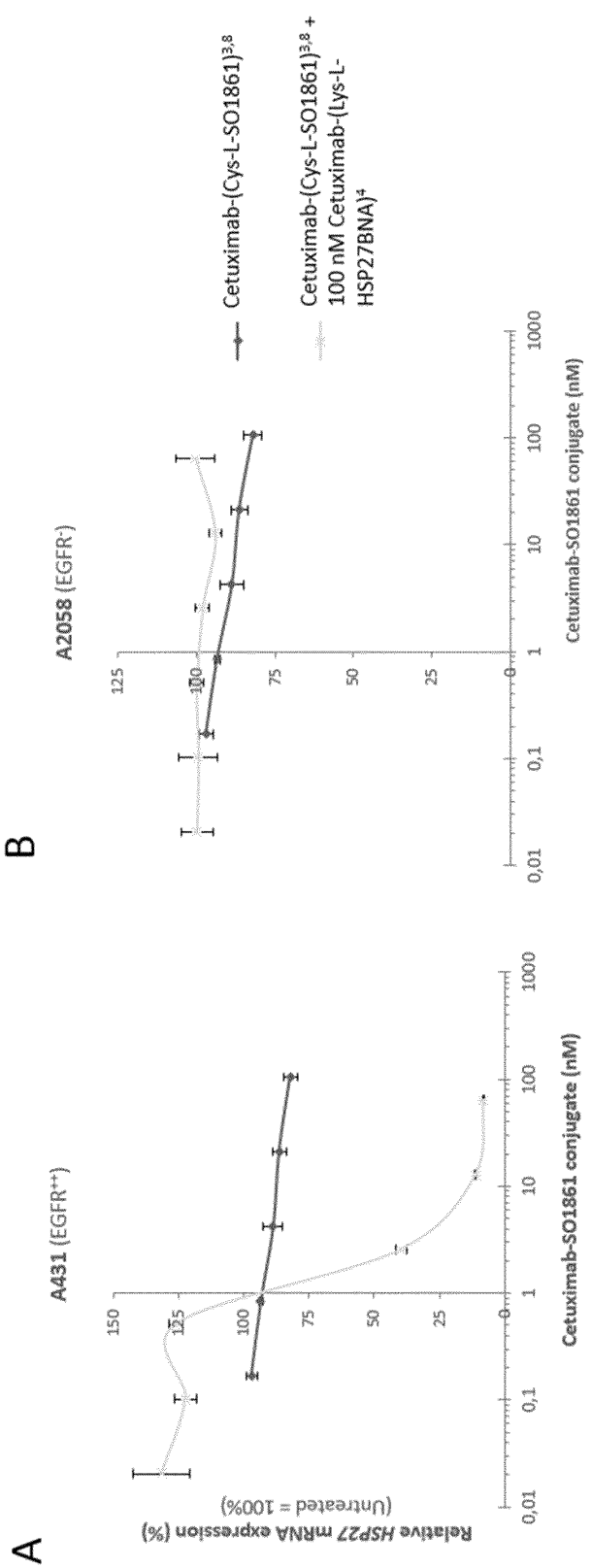

A
A431 (EGFR++)
Relative HSP27 mRNA expression (%)
(Untreated = 100%)
150
125
100
75
50
25
0
0,01
0,1
1
10
100
1000
Cetuximab-SO1861 conjugate (nM)
B
A2058 (EGFR-)
Cetuximab-(Cys-L-SO1861)3,8
Cetuximab-(Cys-L-SO1861)3,8 + 100 nM Cetuximab-(Lys-L-HSP27BNA)4
125
100
75
50
25
0
0,01
0,1
1
10
100
1000
Cetuximab-SO1861 conjugate (nM)

Figure 8-5

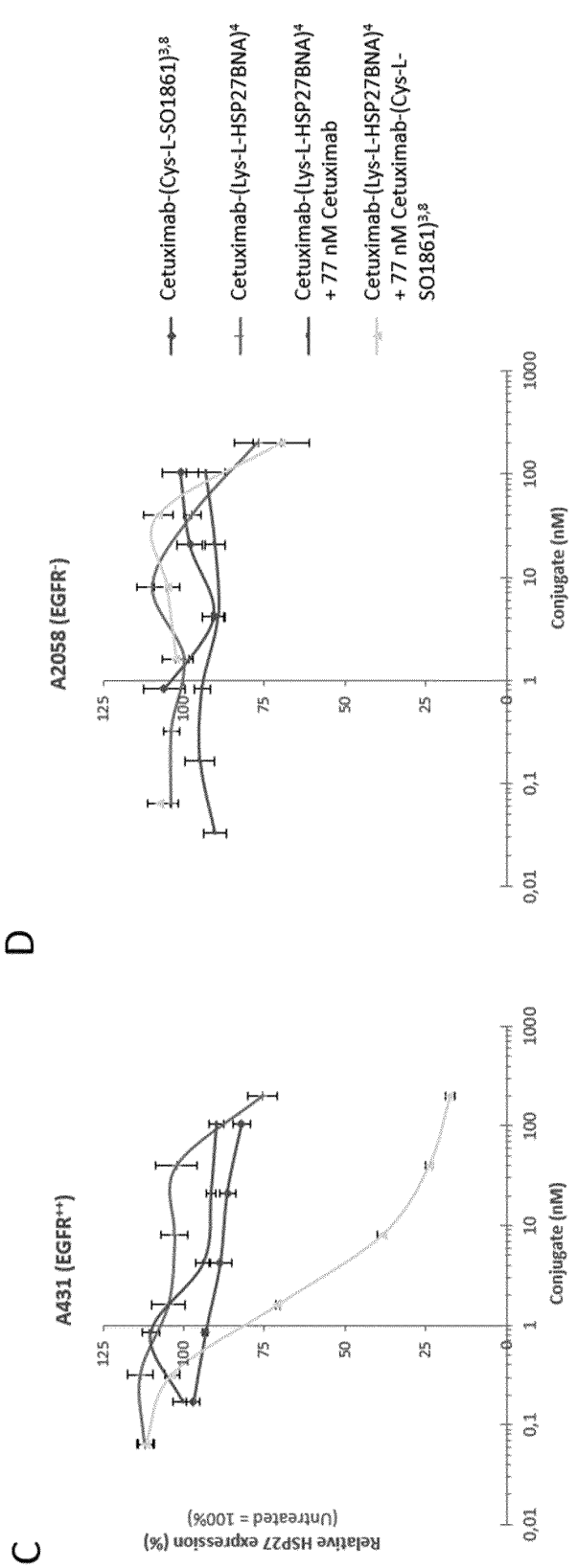

C
A431 (EGFR++)
Relative HSP27 expression (%)
(Untreated = 100%)
125
100
75
50
25
0
0,01
0,1
1
10
100
1000
Conjugate (nM)
D
A2058 (EGFR-)
Cetuximab-(Cys-L-SO1861)3,8
Cetuximab-(Lys-L-HSP27BNA)4
Cetuximab-(Lys-L-HSP27BNA)4 + 77 nM Cetuximab
Cetuximab-(Lys-L-HSP27BNA)4 + 77 nM Cetuximab-(Cys-L-SO1861)3,8

Figure 9-5

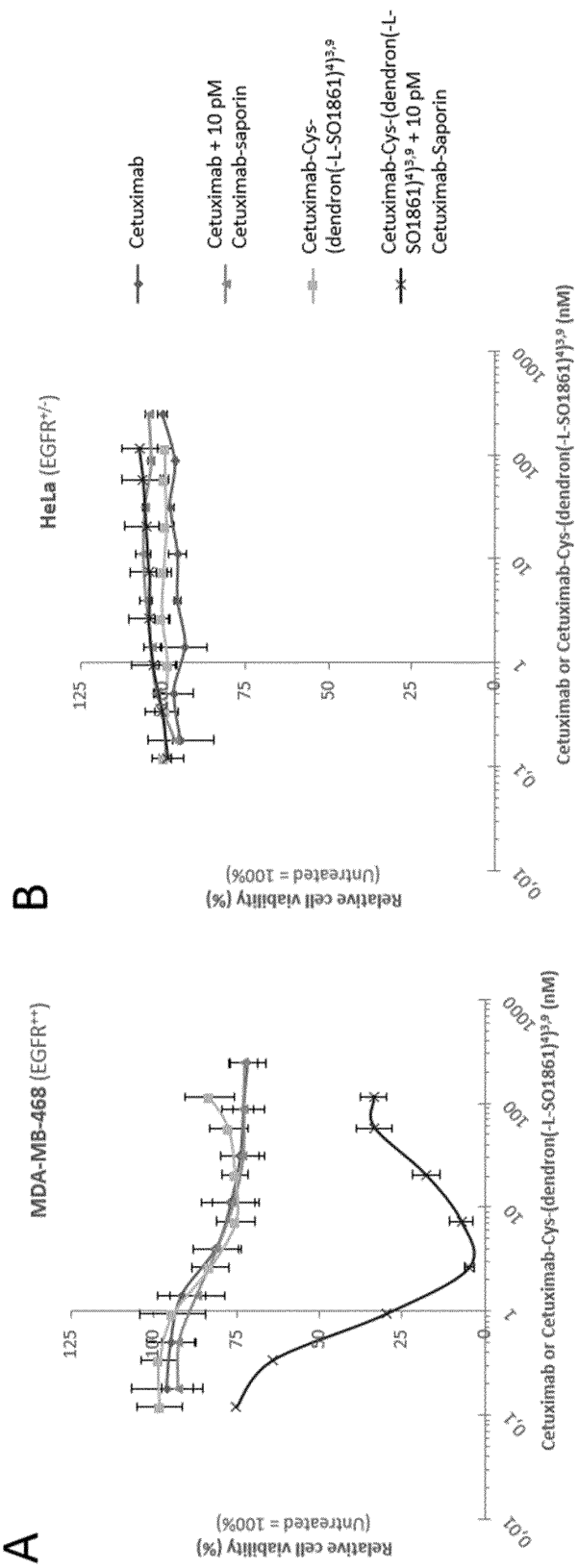

A
MDA-MB-468 (EGFR++)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,01
0,1
1
10
100
1000
Cetuximab or Cetuximab-Cys-(dendron(-L-SO18614)3,9 (nM)
B
HeLa (EGFR+/-)
Cetuximab
Cetuximab + 10 pM Cetuximab-saporin
Cetuximab-Cys-(dendron(-L-SO18614)3,9
Cetuximab-Cys-(dendron(-L-SO18614)3,9 + 10 pM Cetuximab-Saporin

Figure 9-5

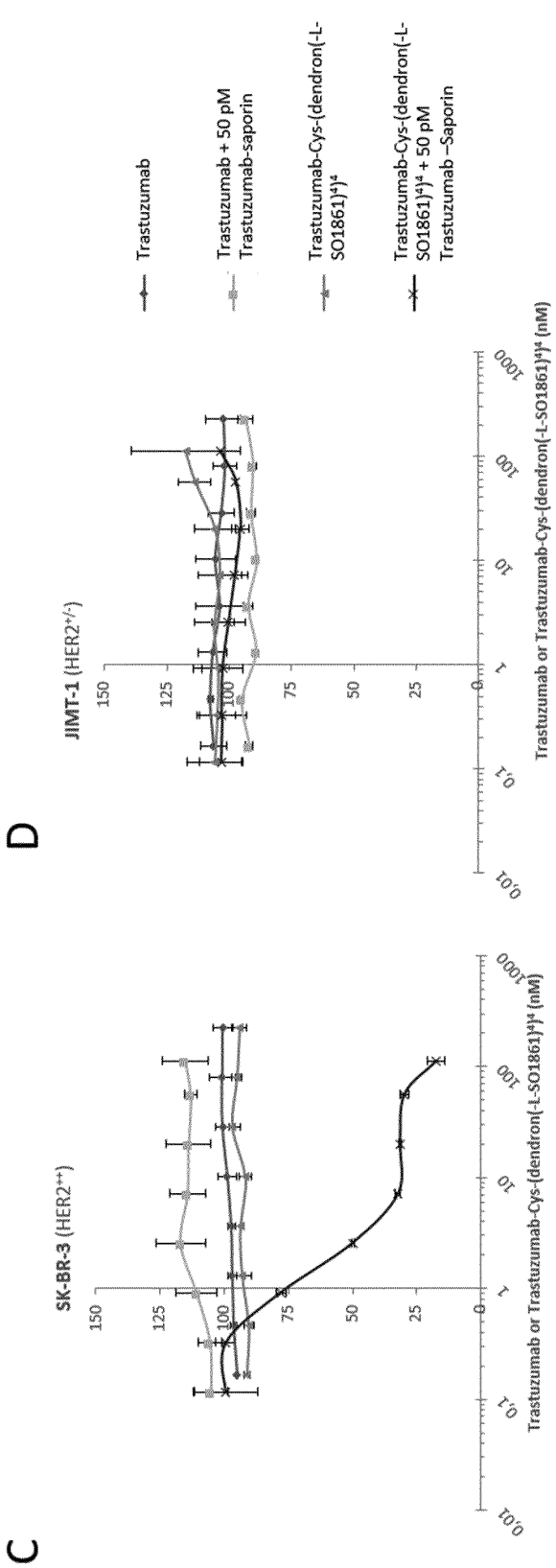

C
SK-BR-3 (HER2++)
D
JIMT-1 (HER2+/-)
Trastuzumab
Trastuzumab + 50 pM Trastuzumab-saporin
Trastuzumab-Cys-(dendron(-L-SO1861)4)4
Trastuzumab-Cys-(dendron(-L-SO1861)4)4 + 50 pM Trastuzumab –Saporin
Trastuzumab or Trastuzumab-Cys-(dendron(-L-SO1861)4)4 (nM)
150
125
100
75
50
25
0
0,01
0,1
1
10
100
1000

Figure 10-5

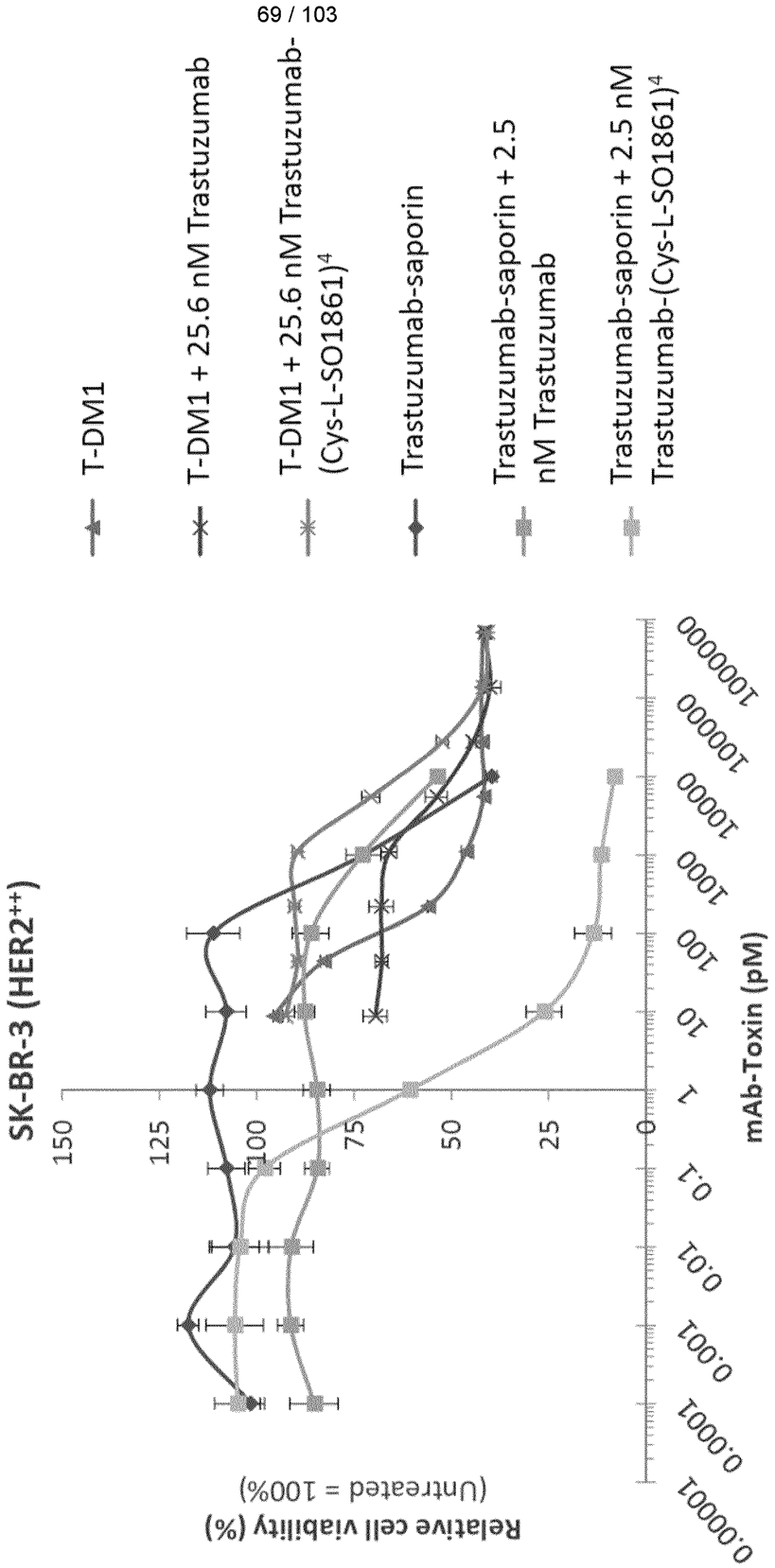

T-DM1
T-DM1 + 25.6 nM Trastuzumab
T-DM1 + 25.6 nM Trastuzumab-(Cys-L-SO1861)4
Trastuzumab-saporin
Trastuzumab-saporin + 2.5 nM Trastuzumab
Trastuzumab-saporin + 2.5 nM Trastuzumab-(Cys-L-SO1861)4
SK-BR-3 (HER2++)
Relative cell viability (%)
(Untreated = 100%)
150
125
100
75
50
25
0
mAb-Toxin (pM)
0.0001
0.001
0.01
0.1
1
10
100
1000
10000
100000
1000000

Figure 11-5

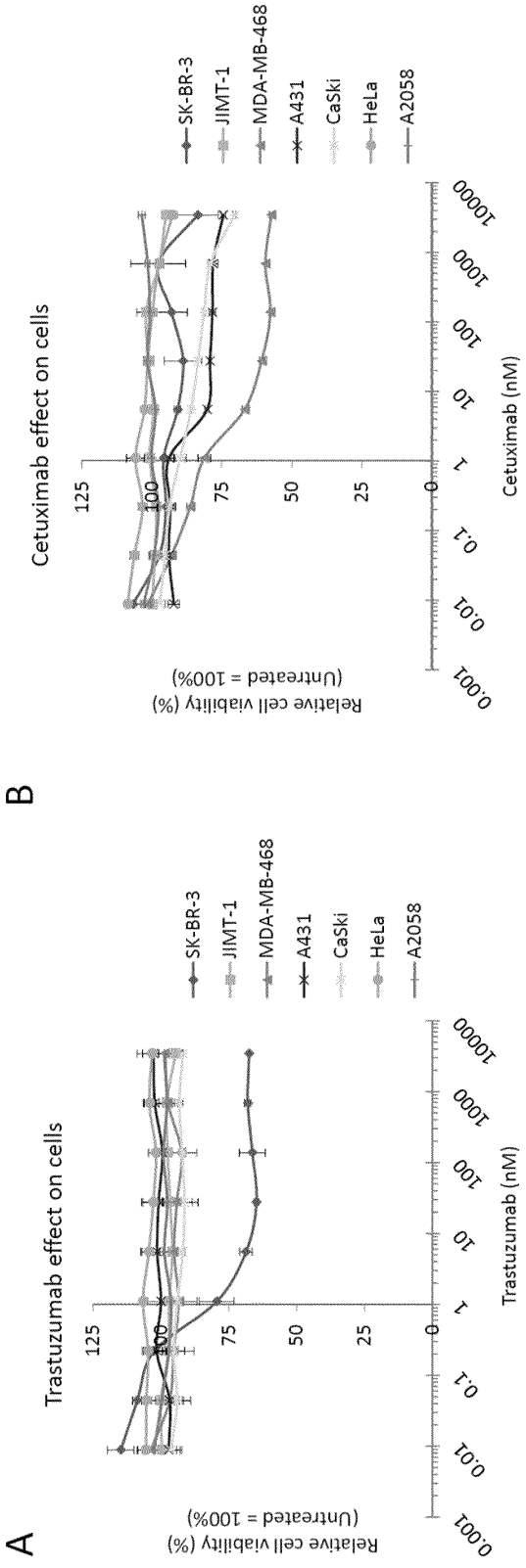

A
Trastuzumab effect on cells
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0.001
0.01
0.1
1
10
100
1000
10000
Trastuzumab (nM)
SK-BR-3
JIMT-1
MDA-MB-468
A431
CaSki
HeLa
A2058
B
Cetuximab effect on cells
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0.001
0.01
0.1
1
10
100
1000
10000
Cetuximab (nM)
SK-BR-3
JIMT-1
MDA-MB-468
A431
CaSki
HeLa
A2058

Figure 11-5

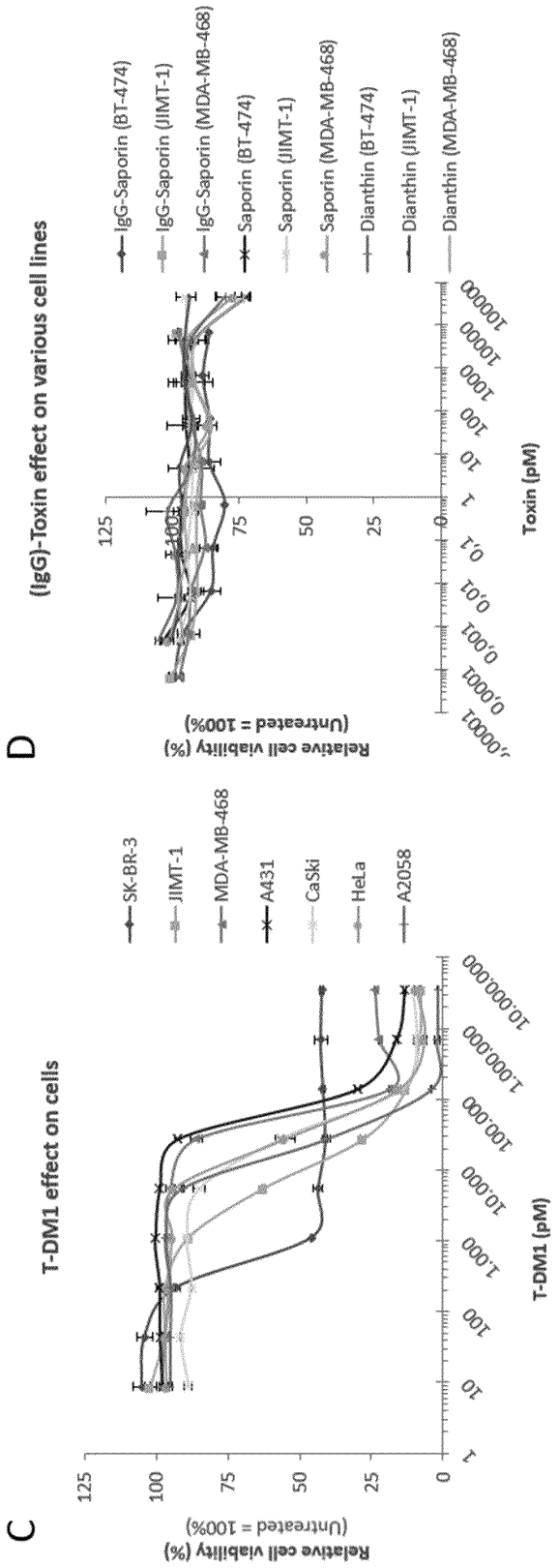

C
T-DM1 effect on cells
Relative cell viability (%)
(Untreated = 100%)
T-DM1 (pM)
SK-BR-3
JIMT-1
MDA-MB-468
A431
CaSki
HeLa
A2058
D
(IgG)-Toxin effect on various cell lines
Relative cell viability (%)
(Untreated = 100%)
Toxin (pM)
IgG-Saporin (BT-474)
IgG-Saporin (JIMT-1)
IgG-Saporin (MDA-MB-468)
Saporin (BT-474)
Saporin (JIMT-1)
Saporin (MDA-MB-468)
Dianthin (BT-474)
Dianthin (JIMT-1)
Dianthin (MDA-MB-468)

Figure 12-5

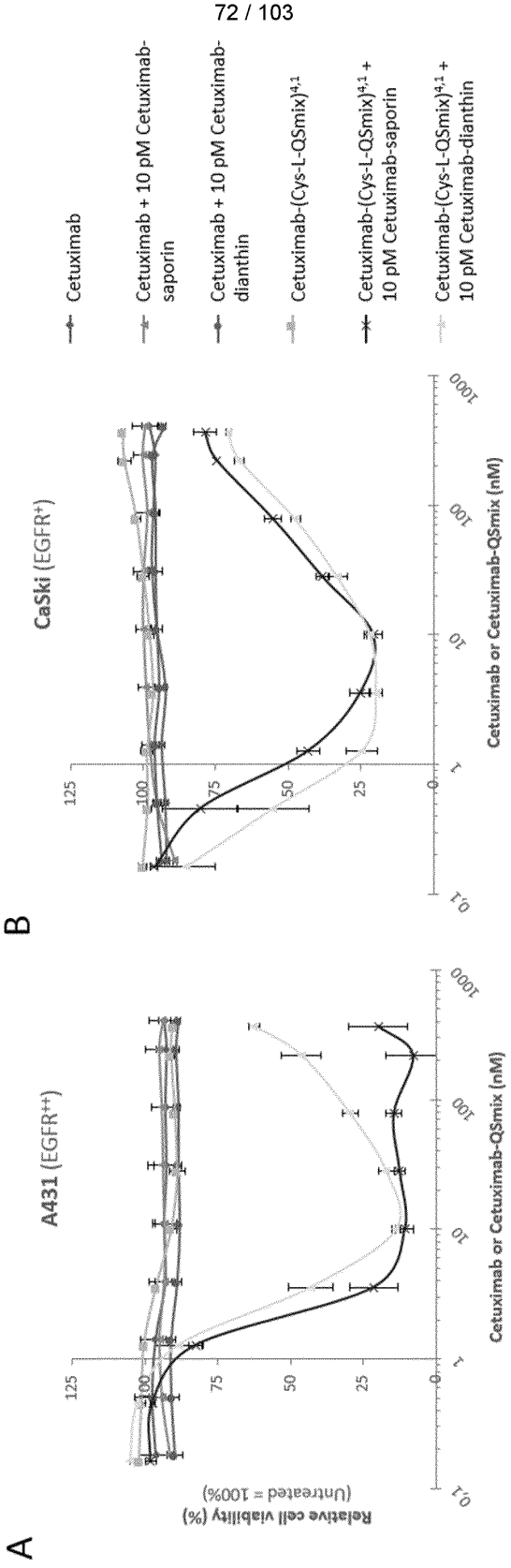

A
A431 (EGFR++)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,1
1
10
100
1000
Cetuximab or Cetuximab-QSmix (nM)
B
CaSki (EGFR+)
Cetuximab
Cetuximab + 10 pM Cetuximab-saporin
Cetuximab + 10 pM Cetuximab-dianthin
Cetuximab-(Cys-L-QSmix)4,1
Cetuximab-(Cys-L-QSmix)4,1 + 10 pM Cetuximab-saporin
Cetuximab-(Cys-L-QSmix)4,1 + 10 pM Cetuximab-dianthin

Figure 12-5

C

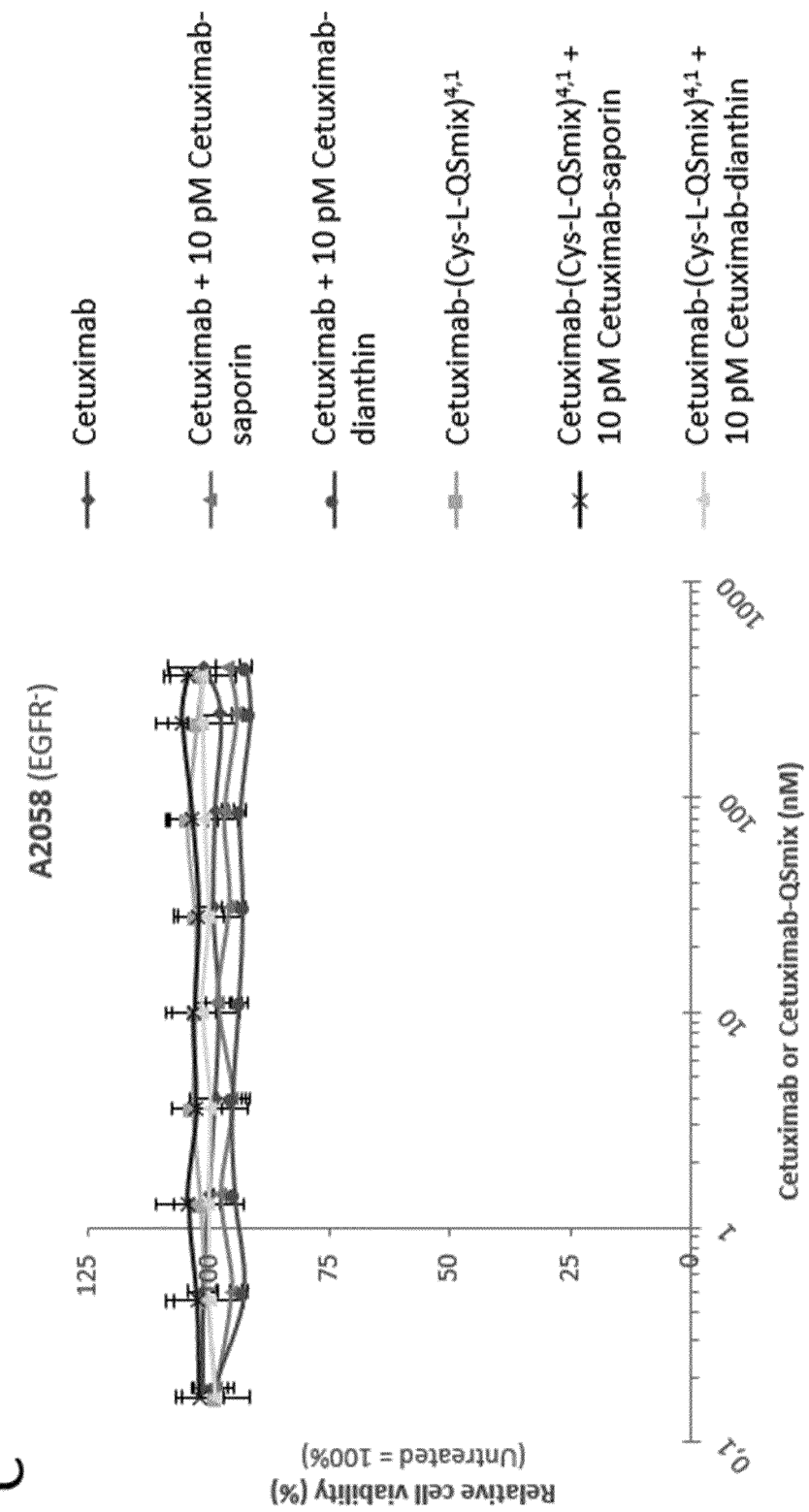

A2058 (EGFR-)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,1
1
10
100
1000
Cetuximab or Cetuximab-QSmix (nM)
Cetuximab
Cetuximab + 10 pM Cetuximab-saporin
Cetuximab + 10 pM Cetuximab-dianthin
Cetuximab-(Cys-L-QSmix)4,1
Cetuximab-(Cys-L-QSmix)4,1 + 10 pM Cetuximab-saporin
Cetuximab-(Cys-L-QSmix)4,1 + 10 pM Cetuximab-dianthin

Figure 13-5

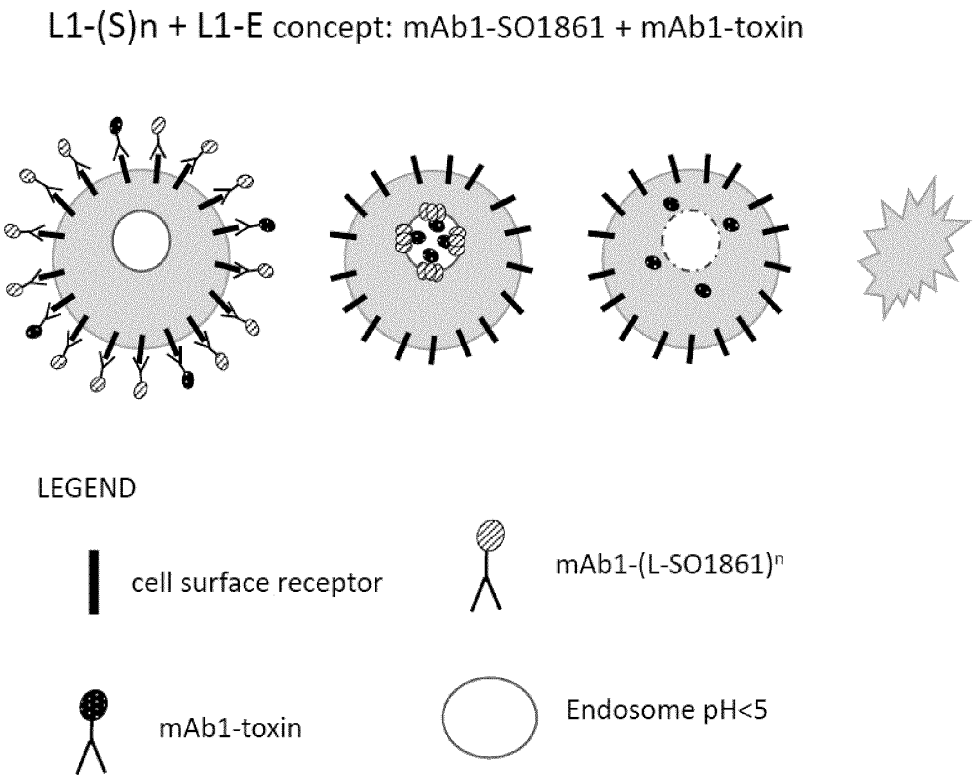


Figure 14-5

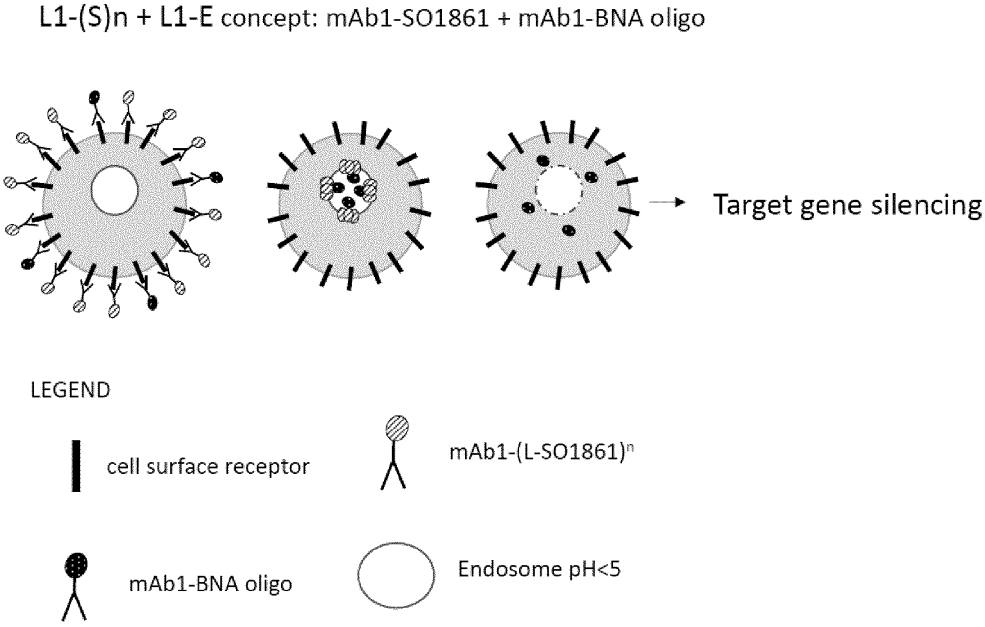


Figure 15-5

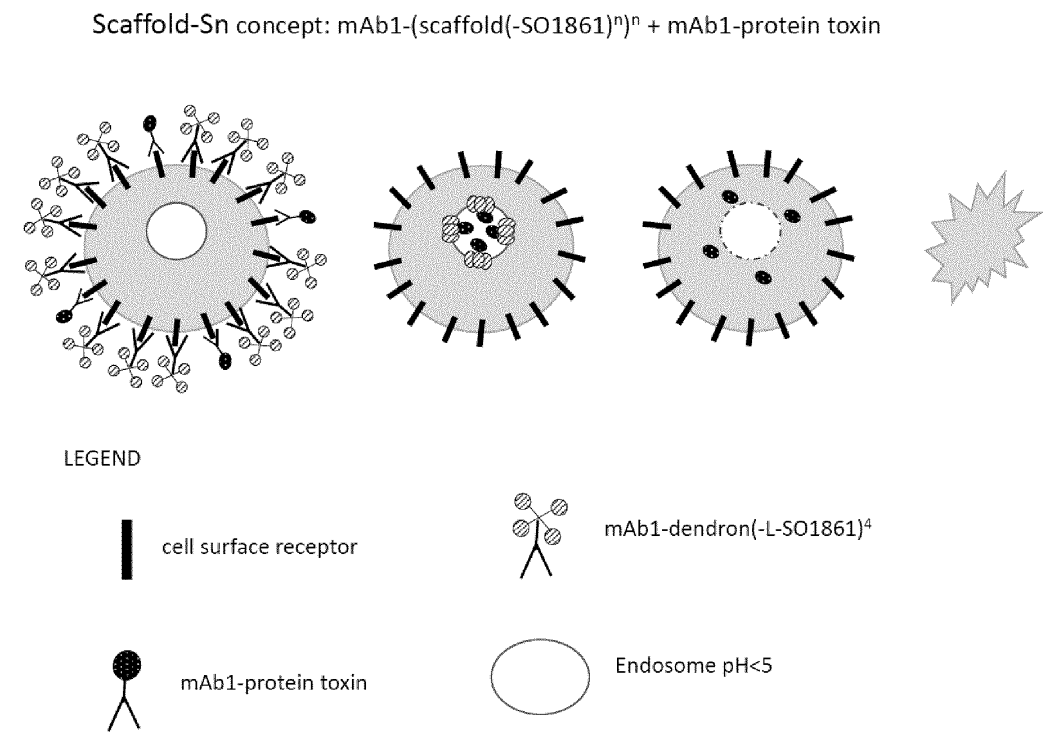

Scaffold-Sn concept: mAb1-(scaffold(-SO1861)n)n + mAb1-protein toxin
LEGEND
cell surface receptor
mAb1-dendron(-L-SO1861)4
mAb1-protein toxin
Endosome pH<5

Fig 1-6

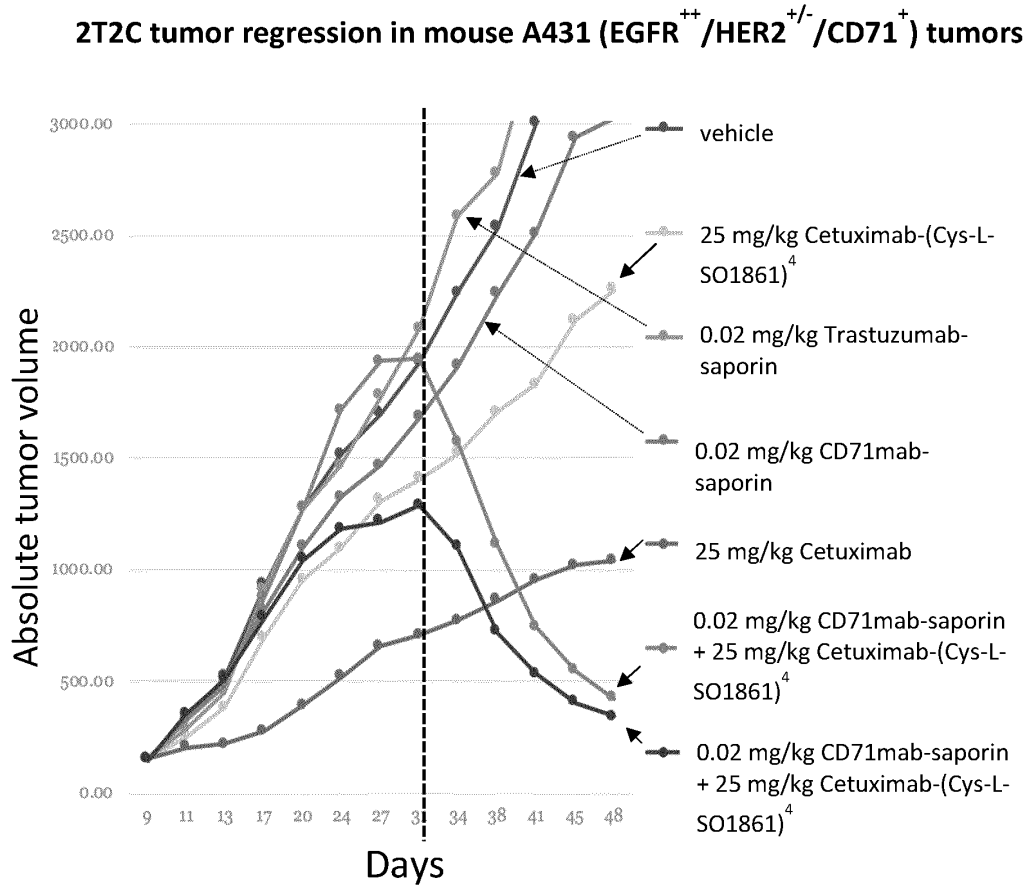

2T2C tumor regression in mouse A431 (EGFR++/HER2+/-/CD71+) tumors
Absolute tumor volume
3000.00
2500.00
2000.00
1500.00
1000.00
500.00
0.00
9 11 13 17 20 24 27 31 34 38 41 45 48
Days
vehicle
25 mg/kg Cetuximab-(Cys-L-SO1861)4
0.02 mg/kg Trastuzumab-saporin
0.02 mg/kg CD71mab-saporin
25 mg/kg Cetuximab
0.02 mg/kg CD71mab-saporin + 25 mg/kg Cetuximab-(Cys-L-SO1861)4
0.02 mg/kg CD71mab-saporin + 25 mg/kg Cetuximab-(Cys-L-SO1861)4

Fig 2-6

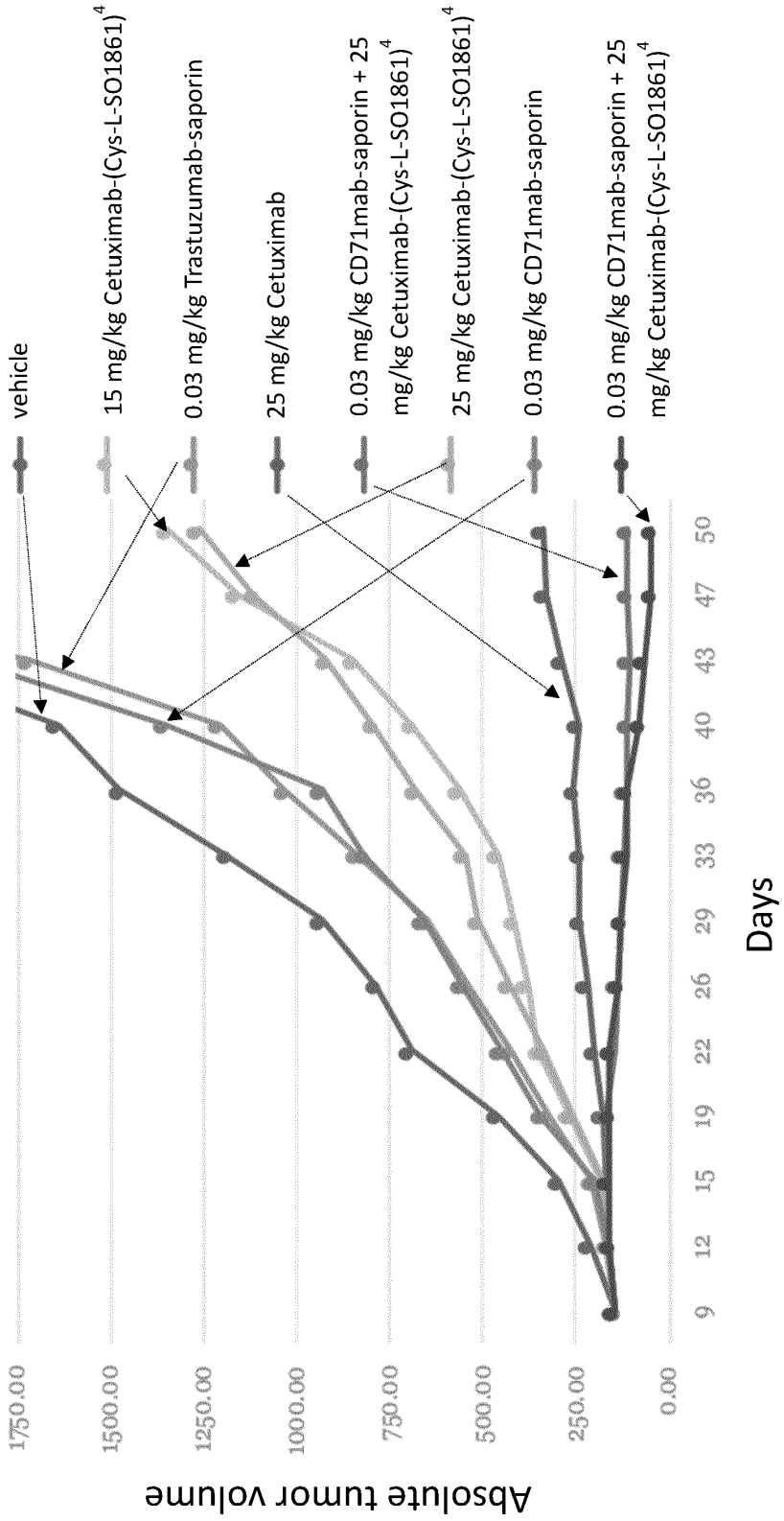
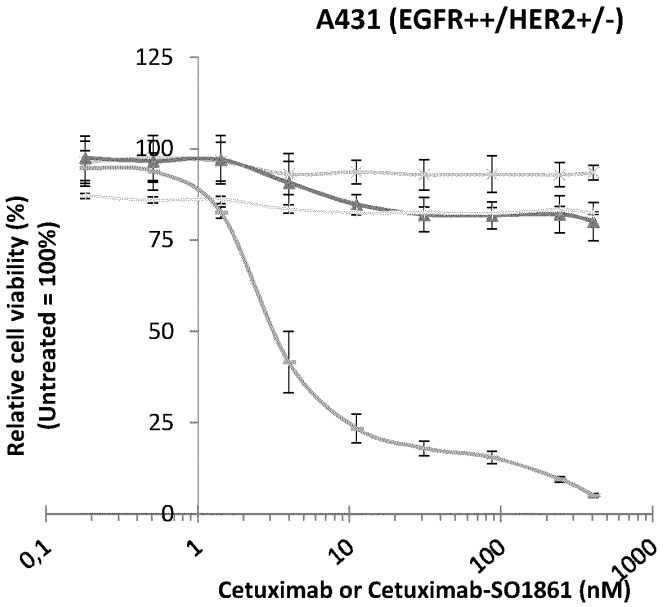

2T2C tumor regression and eradication in mouse A431 (EGFR++/HER2+/-/CD71+) tumors
vehicle
15 mg/kg Cetuximab-(Cys-L-SO1861)4
0.03 mg/kg Trastuzumab-saporin
25 mg/kg Cetuximab
0.03 mg/kg CD71mab-saporin + 25 mg/kg Cetuximab-(Cys-L-SO1861)4
25 mg/kg Cetuximab-(Cys-L-SO1861)4
0.03 mg/kg CD71mab-saporin
0.03 mg/kg CD71mab-saporin + 25 mg/kg Cetuximab-(Cys-L-SO1861)4
Absolute tumor volume
1750.00
1500.00
1250.00
1000.00
750.00
500.00
250.00
0.00
9 12 15 19 22 26 29 33 36 40 43 47 50
Days

Figure 3-6

A


A431 (EGFR++/HER2+/-)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,1
1
10
100
1000
Cetuximab or Cetuximab-SO1861 (nM)

B

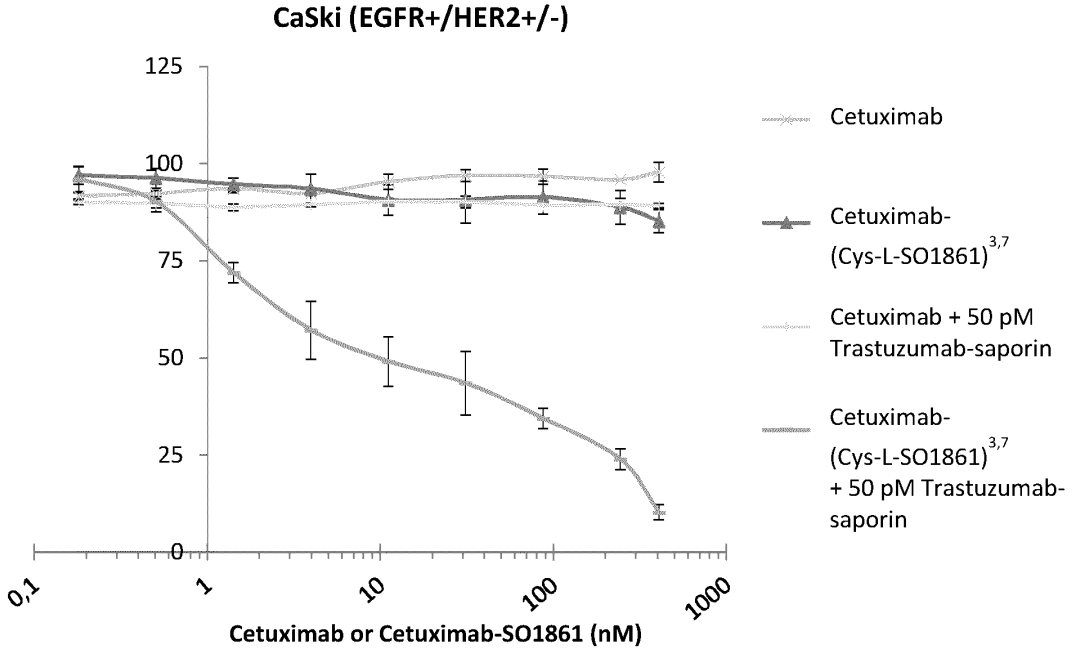
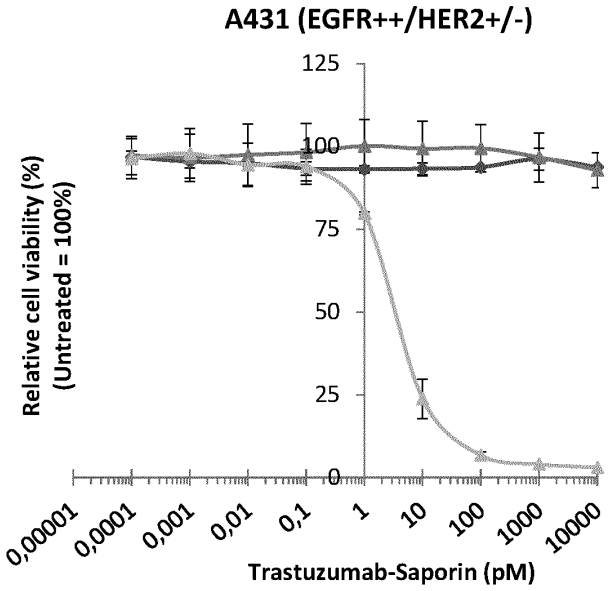

CaSki (EGFR+/HER2+/-)
125
100
75
50
25
0
0,1
1
10
100
1000
Cetuximab or Cetuximab-SO1861 (nM)
Cetuximab
Cetuximab-(Cys-L-SO1861)3,7
Cetuximab + 50 pM Trastuzumab-saporin
Cetuximab-(Cys-L-SO1861)3,7 + 50 pM Trastuzumab-saporin

Figure 3-6

C


A431 (EGFR++/HER2+/-)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,00001
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
Trastuzumab-Saporin (pM)

D

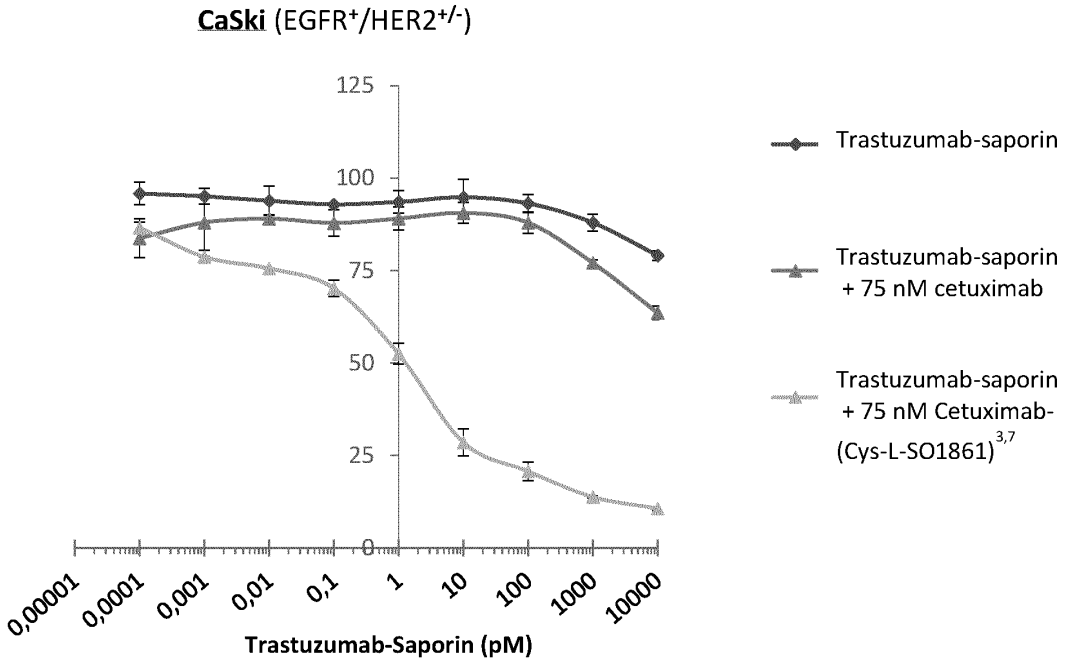
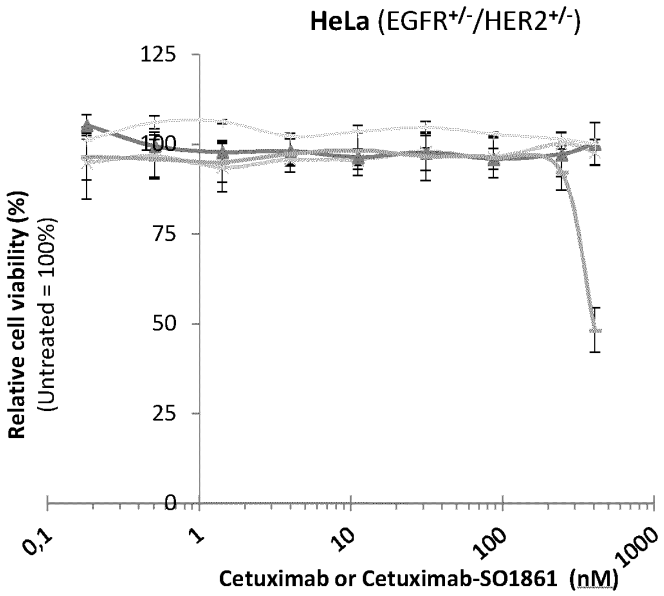

CaSki (EGFR+/HER2+/-)
125
100
75
50
25
0
0,00001
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
Trastuzumab-Saporin (pM)
Trastuzumab-saporin
Trastuzumab-saporin + 75 nM cetuximab
Trastuzumab-saporin + 75 nM Cetuximab-(Cys-L-SO1861)3,7

Figure 4-6

A


HeLa (EGFR+/-/HER2+/-)
125
100
75
50
25
0
Relative cell viability (%)
(Untreated = 100%)
0,1
1
10
100
1000
Cetuximab or Cetuximab-SO1861 (nM)

B

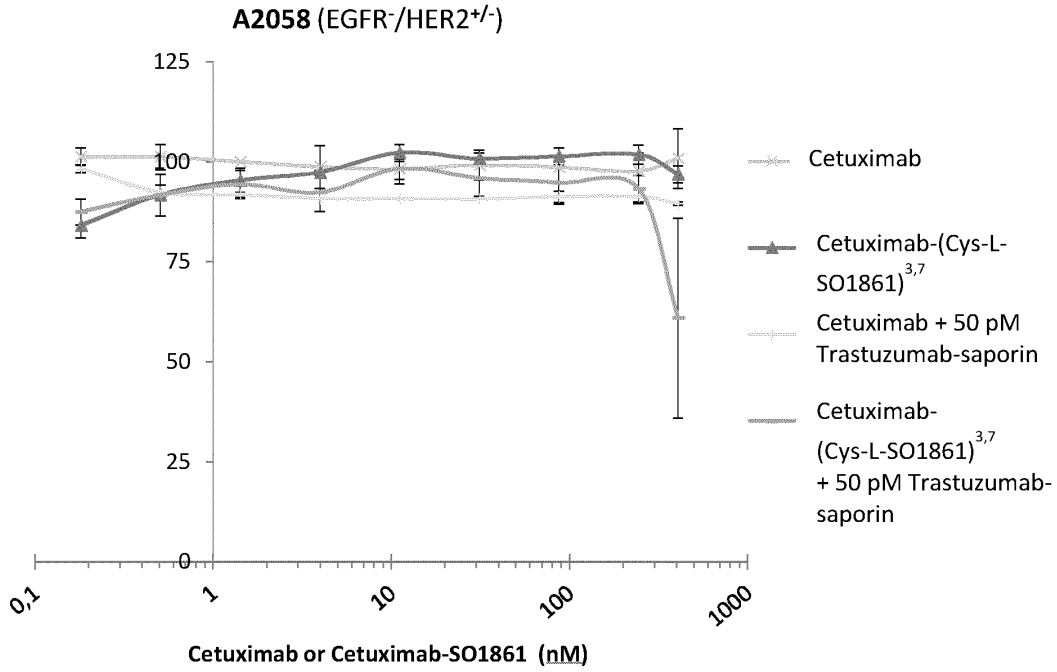
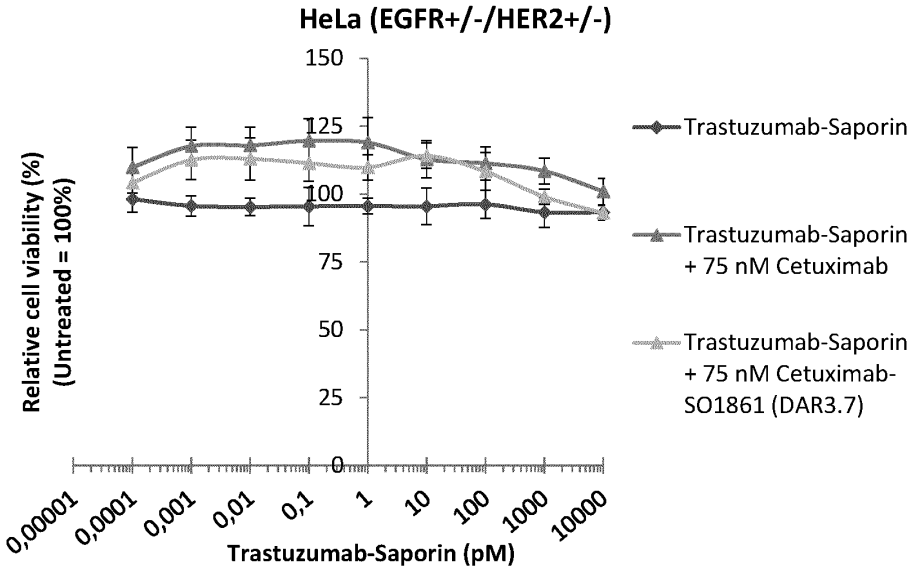

A2058 (EGFR-/HER2+/-)
125
100
75
50
25
0
0,1
1
10
100
1000
Cetuximab or Cetuximab-SO1861 (nM)
Cetuximab
Cetuximab-(Cys-L-SO1861)3,7
Cetuximab + 50 pM Trastuzumab-saporin
Cetuximab-(Cys-L-SO1861)3,7 + 50 pM Trastuzumab-saporin

Figure 4-6

C


HeLa (EGFR+/-/HER2+/-)
Relative cell viability (%)
(Untreated = 100%)
150
125
100
75
50
25
0
0,00001
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
Trastuzumab-Saporin (pM)
Trastuzumab-Saporin
Trastuzumab-Saporin + 75 nM Cetuximab
Trastuzumab-Saporin + 75 nM Cetuximab-SO1861 (DAR3.7)

D

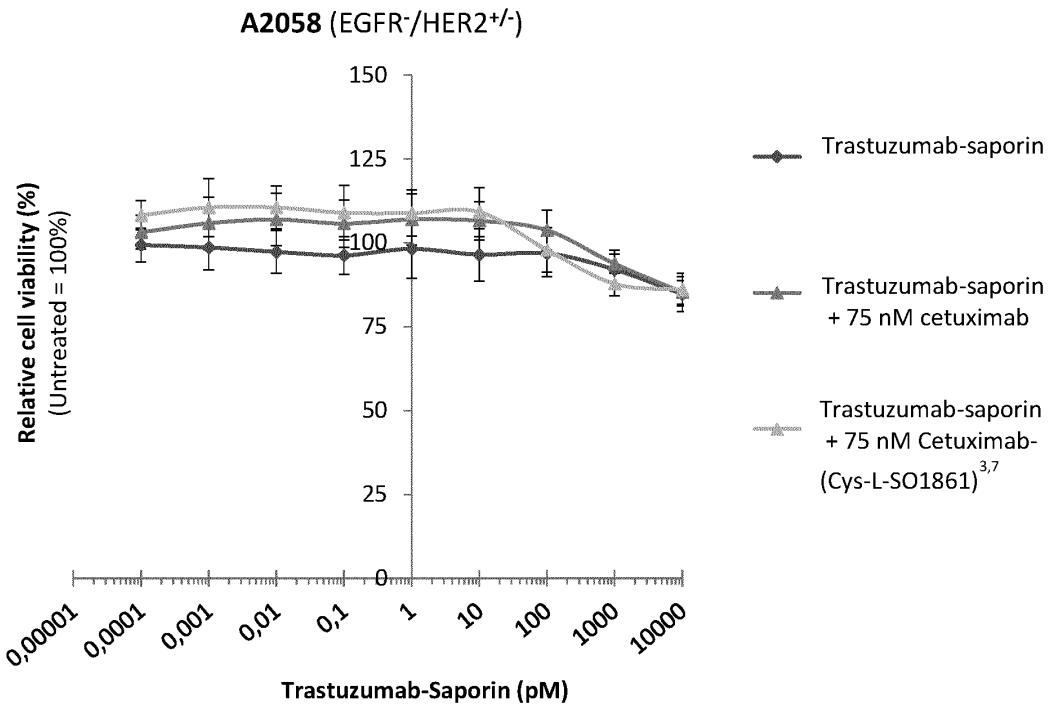
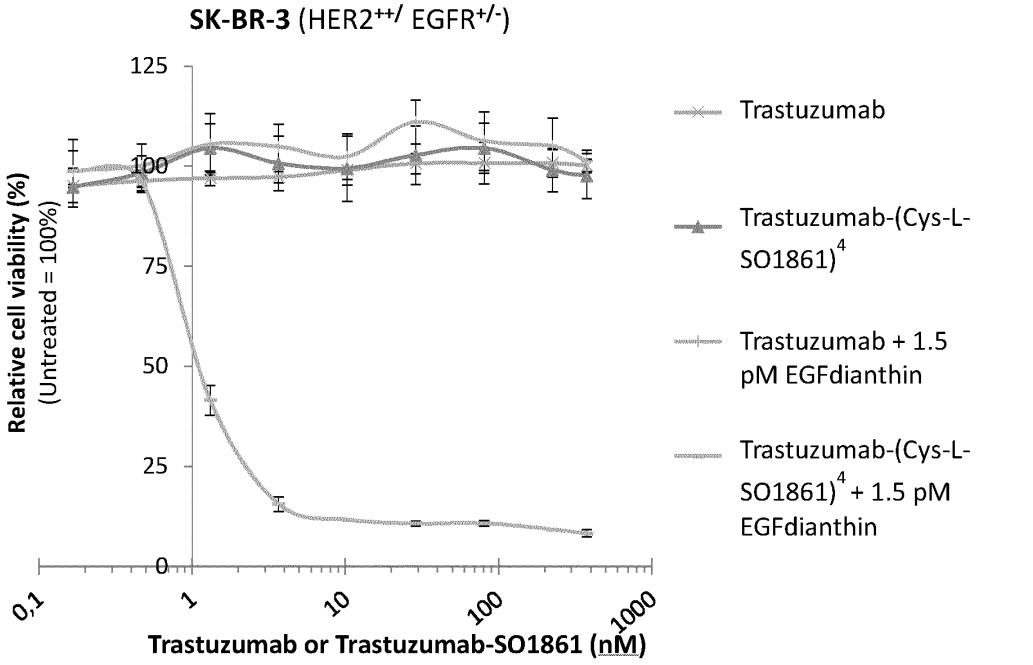

A2058 (EGFR-/HER2+/-)
Relative cell viability (%)
(Untreated = 100%)
150
125
100
75
50
25
0
0,00001
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
Trastuzumab-Saporin (pM)
Trastuzumab-saporin
Trastuzumab-saporin + 75 nM cetuximab
Trastuzumab-saporin + 75 nM Cetuximab-(Cys-L-SO1861)3,7

Figure 5-6

A


SK-BR-3 (HER2++/ EGFR+/-)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,1
1
10
100
1000
Trastuzumab or Trastuzumab-SO1861 (nM)
Trastuzumab
Trastuzumab-(Cys-L-SO1861)4
Trastuzumab + 1.5 pM EGFdianthin
Trastuzumab-(Cys-L-SO1861)4 + 1.5 pM EGFdianthin

B

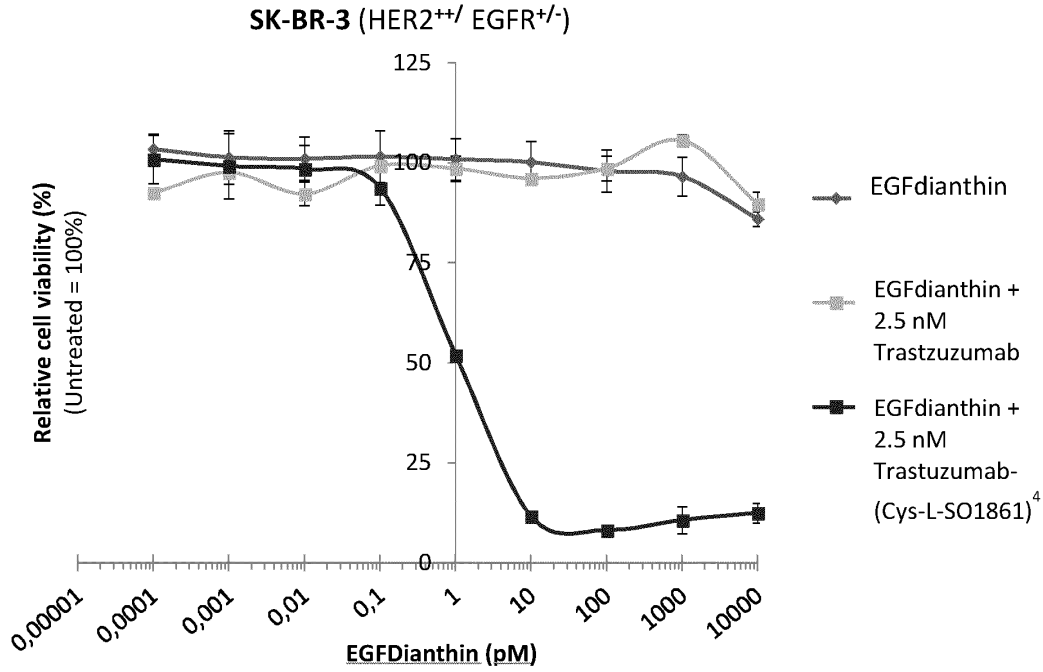
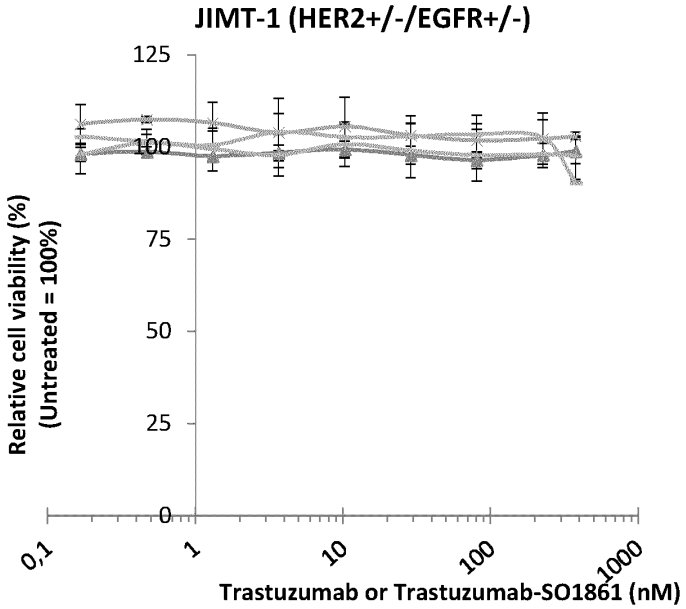

SK-BR-3 (HER2++/ EGFR+/-)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,00001
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
EGFDianthin (pM)
EGFdianthin
EGFdianthin + 2.5 nM Trastzuzumab
EGFdianthin + 2.5 nM Trastuzumab-(Cys-L-SO1861)4

Figure 6-6

A


JIMT-1 (HER2+/-/EGFR+/-)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,1
1
10
100
1000
Trastuzumab or Trastuzumab-SO1861 (nM)

B

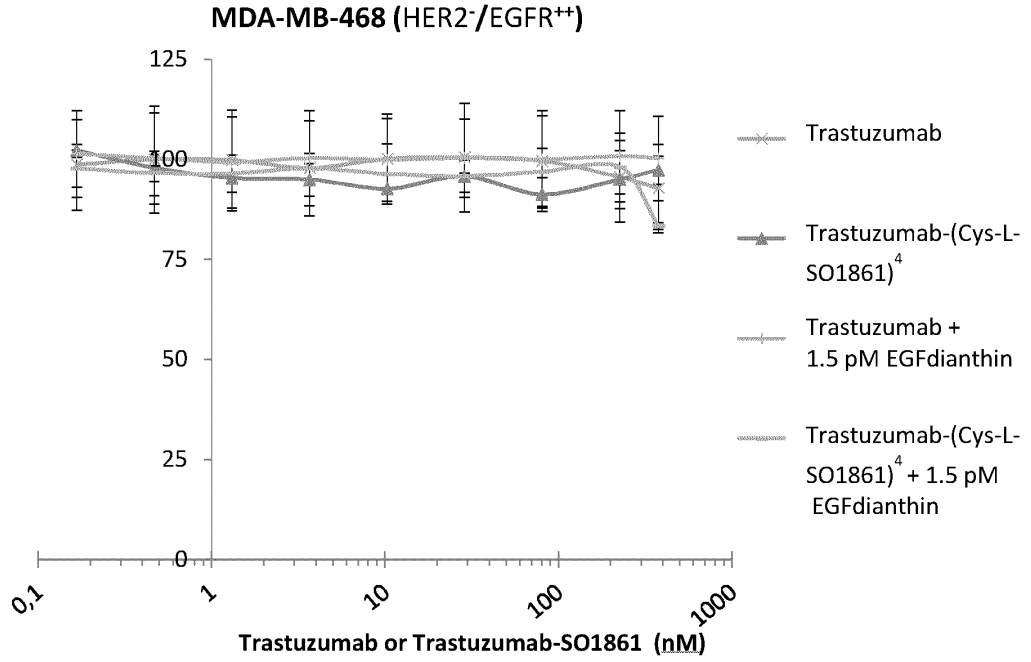
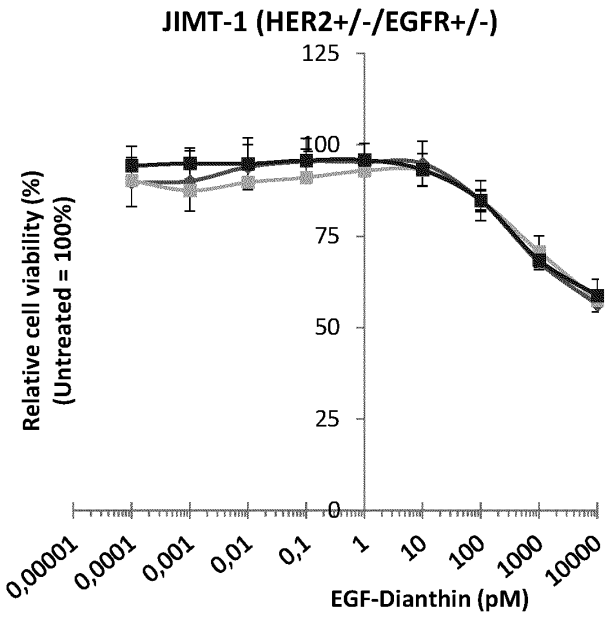

MDA-MB-468 (HER2-/EGFR++)
125
100
75
50
25
0
0,1
1
10
100
1000
Trastuzumab or Trastuzumab-SO1861 (nM)
Trastuzumab
Trastuzumab-(Cys-L-SO1861)4
Trastuzumab + 1.5 pM EGFdianthin
Trastuzumab-(Cys-L-SO1861)4 + 1.5 pM EGFdianthin

Figure 6-6

C


JIMT-1 (HER2+/-/EGFR+/-)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,00001
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
EGF-Dianthin (pM)

D

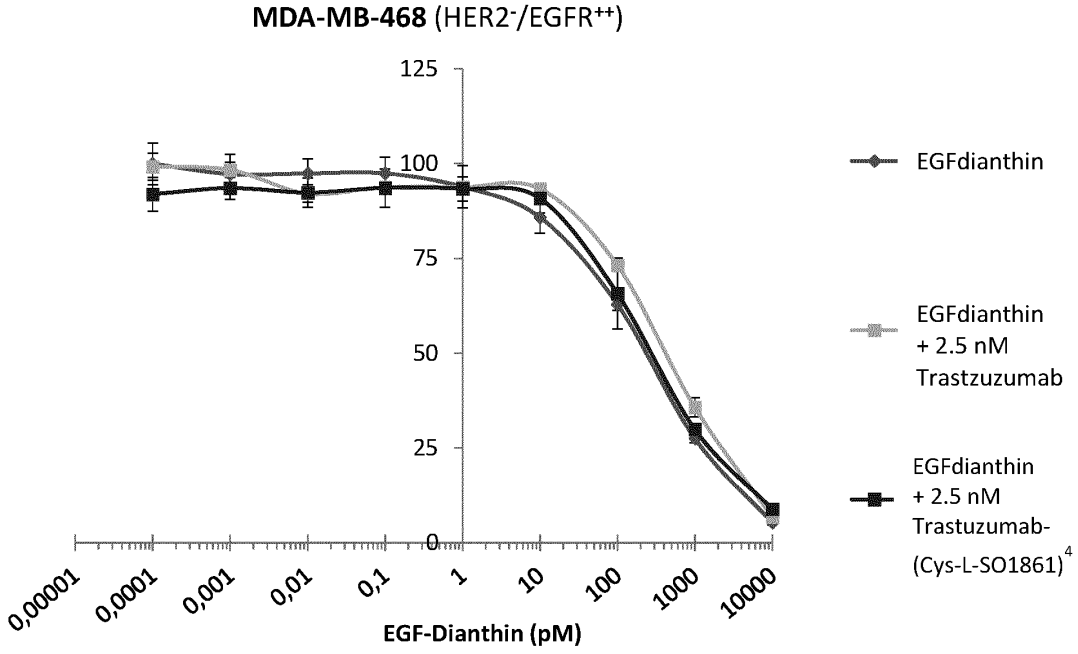
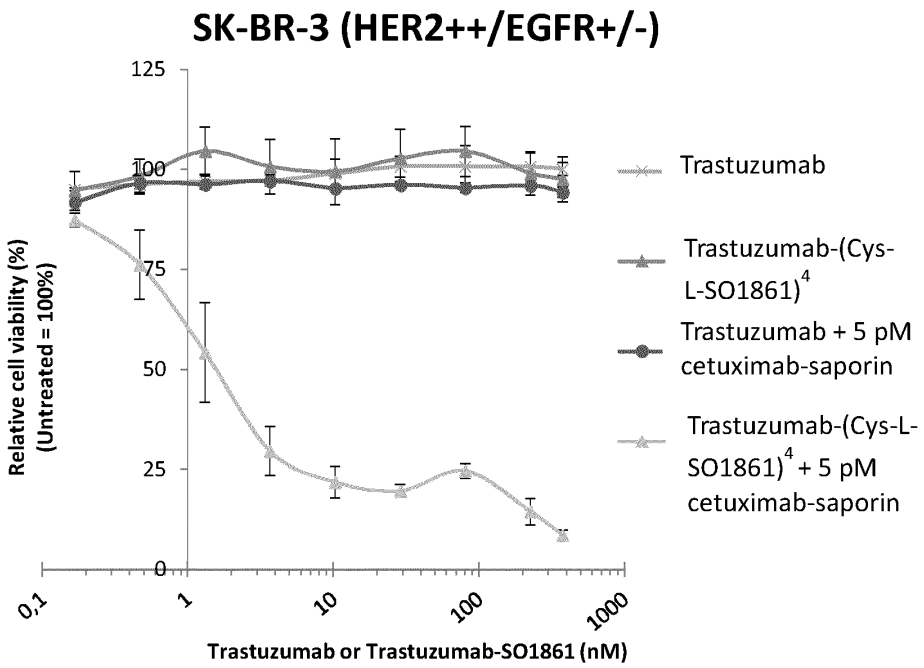

MDA-MB-468 (HER2-/EGFR++)
125
100
75
50
25
0
0,00001
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
EGF-Dianthin (pM)
EGFdianthin
EGFdianthin + 2.5 nM Trastzuzumab
EGFdianthin + 2.5 nM Trastuzumab-(Cys-L-SO1861)4

Figure 7-6

A


SK-BR-3 (HER2++/EGFR+/-)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,1
1
10
100
1000
Trastuzumab or Trastuzumab-SO1861 (nM)
Trastuzumab
Trastuzumab-(Cys-L-SO1861)4
Trastuzumab + 5 pM cetuximab-saporin
Trastuzumab-(Cys-L-SO1861)4 + 5 pM cetuximab-saporin

B

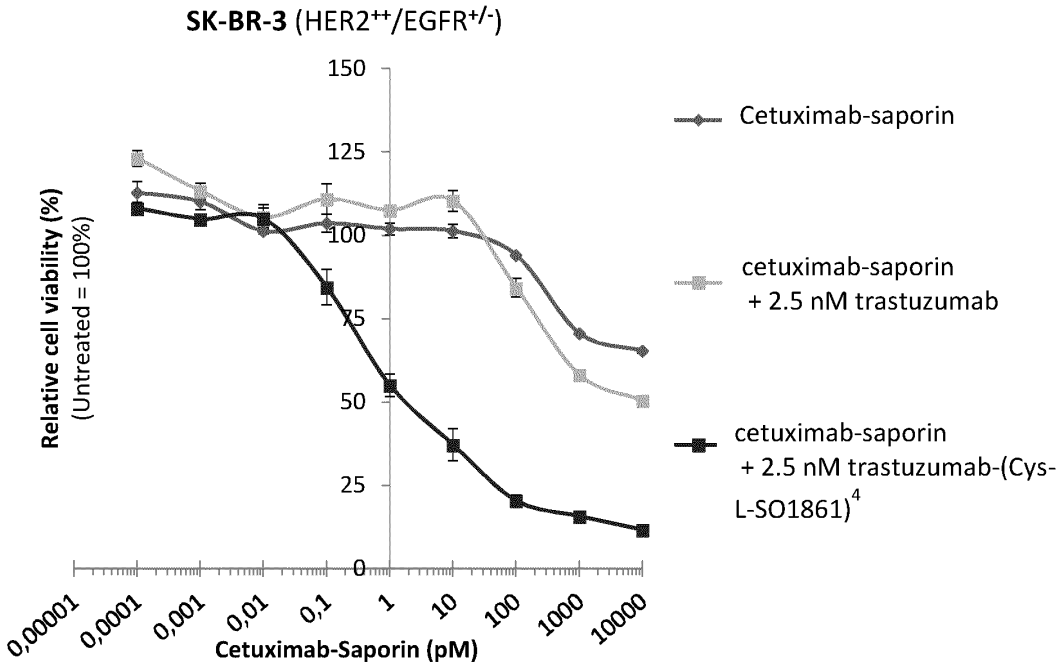
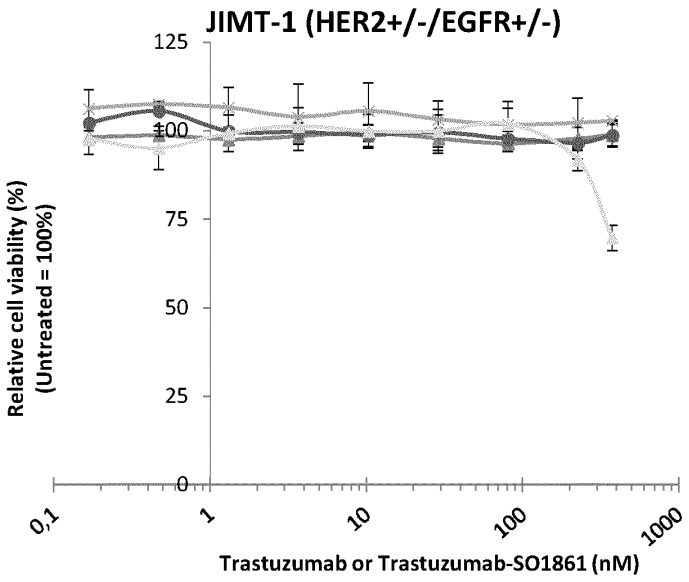

SK-BR-3 (HER2++/EGFR+/-)
Relative cell viability (%)
(Untreated = 100%)
150
125
100
75
50
25
0
0,00001
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
Cetuximab-Saporin (pM)
Cetuximab-saporin
cetuximab-saporin + 2.5 nM trastuzumab
cetuximab-saporin + 2.5 nM trastuzumab-(Cys-L-SO1861)4

Figure 8-6

A


JIMT-1 (HER2+/-/EGFR+/-)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,1
1
10
100
1000
Trastuzumab or Trastuzumab-SO1861 (nM)

B

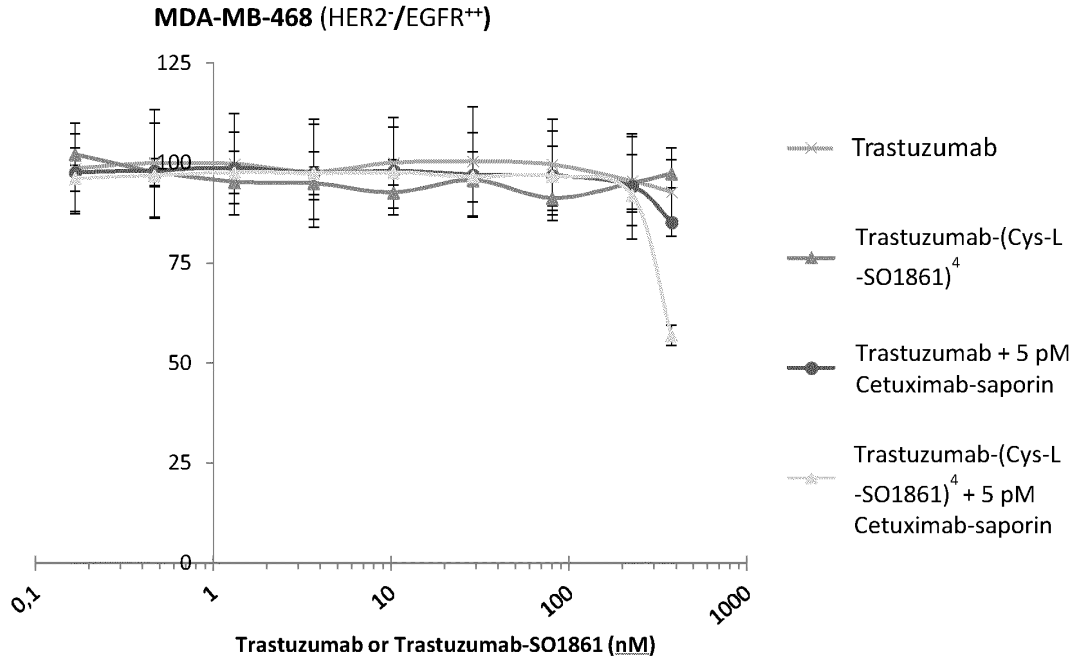
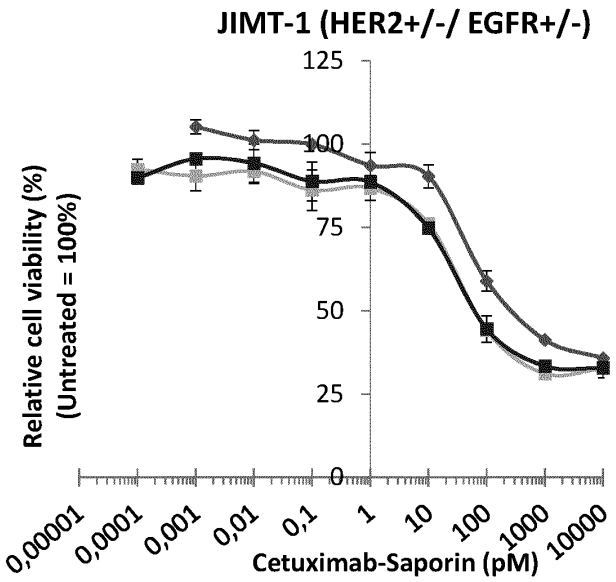

MDA-MB-468 (HER2-/EGFR++)
125
100
75
50
25
0
0,1
1
10
100
1000
Trastuzumab or Trastuzumab-SO1861 (nM)
Trastuzumab
Trastuzumab-(Cys-L-SO1861)4
Trastuzumab + 5 pM Cetuximab-saporin
Trastuzumab-(Cys-L-SO1861)4 + 5 pM Cetuximab-saporin

Figure 8-6

C


JIMT-1 (HER2+/-/ EGFR+/-)
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,00001
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
Cetuximab-Saporin (pM)

D

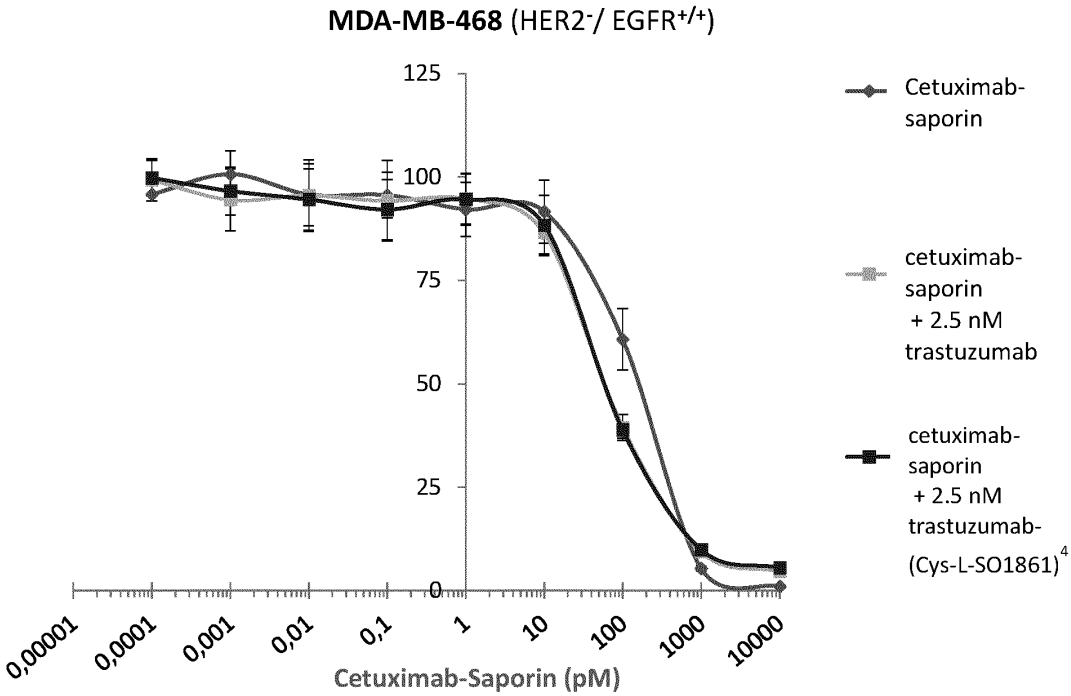
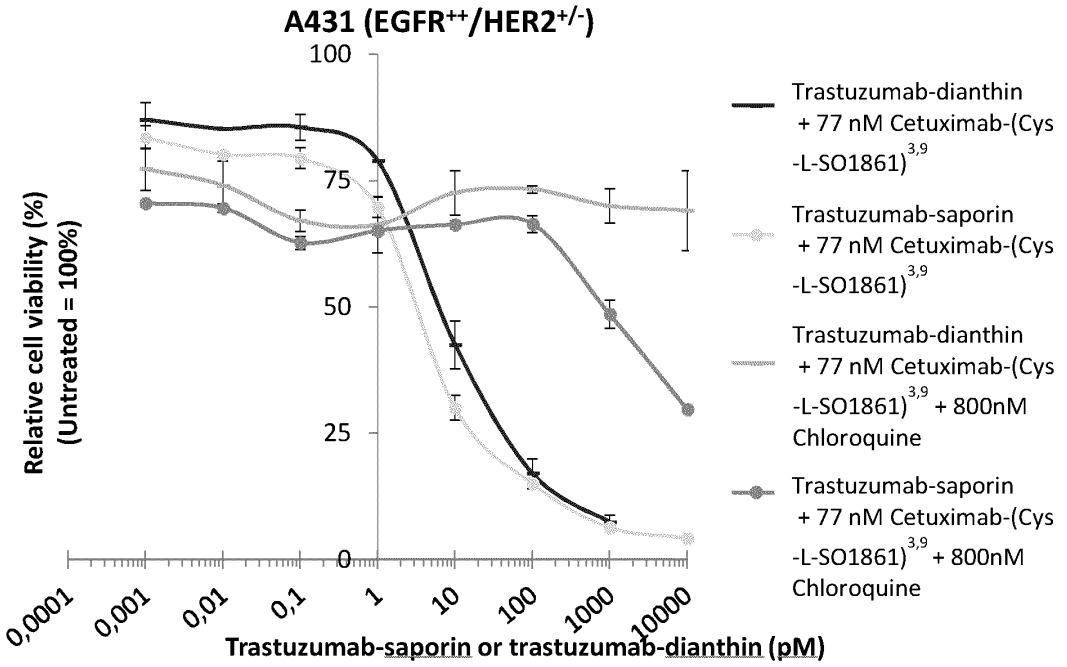

MDA-MB-468 (HER2- / EGFR+/+)
125
100
75
50
25
0
0,00001
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
Cetuximab-Saporin (pM)
Cetuximab-saporin
cetuximab-saporin + 2.5 nM trastuzumab
cetuximab-saporin + 2.5 nM trastuzumab-(Cys-L-SO1861)4

Figure 9-6

A


A431 (EGFR++/HER2+/-)
Relative cell viability (%) (Untreated = 100%)
100
75
50
25
0
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
Trastuzumab-saporin or trastuzumab-dianthin (pM)
Trastuzumab-dianthin + 77 nM Cetuximab-(Cys-L-SO1861)3,9
Trastuzumab-saporin + 77 nM Cetuximab-(Cys-L-SO1861)3,9
Trastuzumab-dianthin + 77 nM Cetuximab-(Cys-L-SO1861)3,9 + 800nM Chloroquine
Trastuzumab-saporin + 77 nM Cetuximab-(Cys-L-SO1861)3,9 + 800nM Chloroquine

B

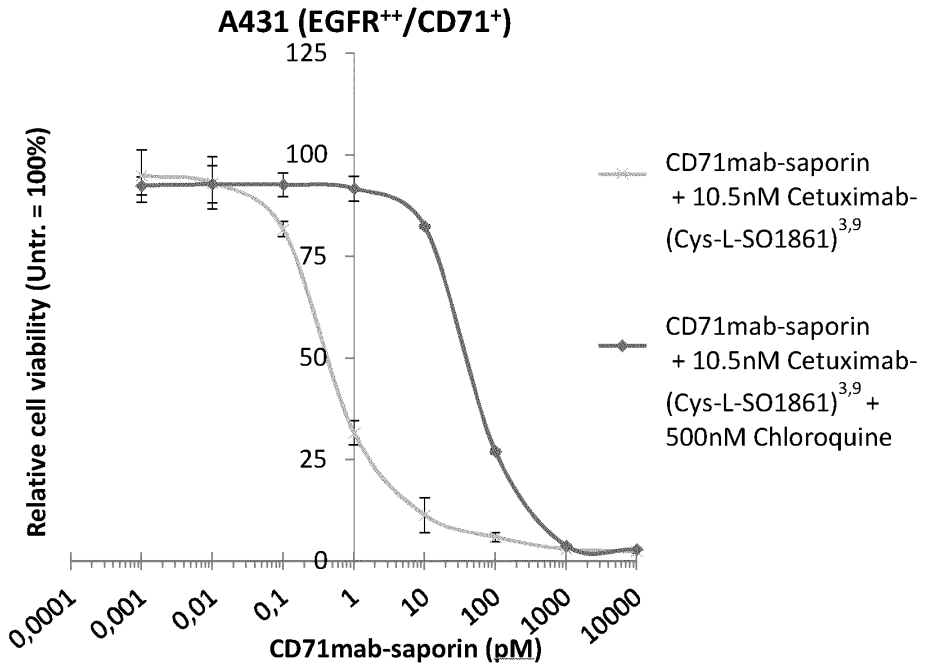
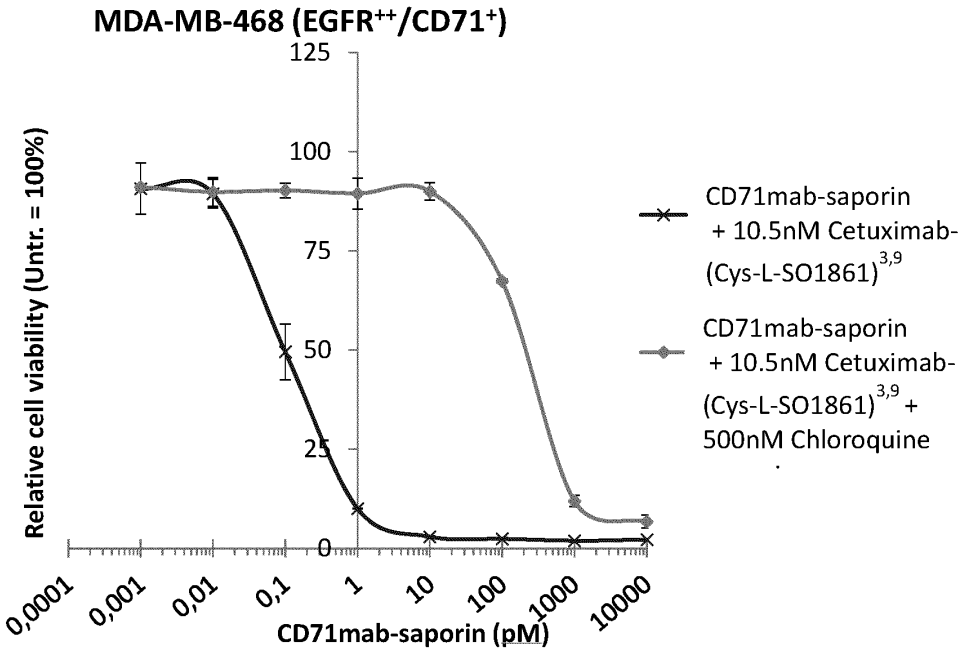

A431 (EGFR++/CD71+)
Relative cell viability (Untr. = 100%)
125
100
75
50
25
0
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
CD71mab-saporin (pM)
CD71mab-saporin + 10.5nM Cetuximab-(Cys-L-SO1861)3,9
CD71mab-saporin + 10.5nM Cetuximab-(Cys-L-SO1861)3,9 + 500nM Chloroquine

Figure 9-6

C


MDA-MB-468 (EGFR++/CD71+)
Relative cell viability (Untr. = 100%)
125
100
75
50
25
0
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
CD71mab-saporin (pM)
CD71mab-saporin + 10.5nM Cetuximab-(Cys-L-SO1861)3,9
CD71mab-saporin + 10.5nM Cetuximab-(Cys-L-SO1861)3,9 + 500nM Chloroquine

D

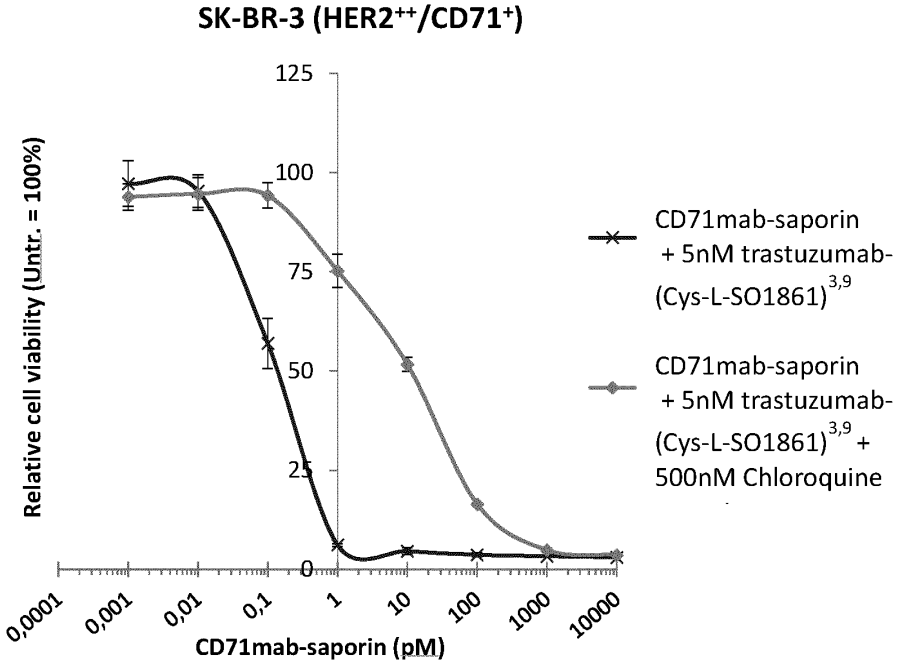
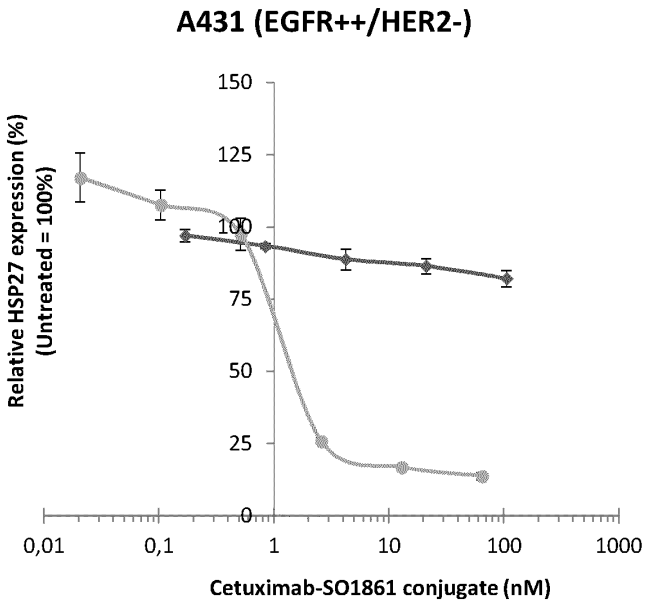

SK-BR-3 (HER2++/CD71+)
Relative cell viability (Untr. = 100%)
125
100
75
50
25
0
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
CD71mab-saporin (pM)
CD71mab-saporin + 5nM trastuzumab-(Cys-L-SO1861)3,9
CD71mab-saporin + 5nM trastuzumab-(Cys-L-SO1861)3,9 + 500nM Chloroquine

Figure 10-6

A



B

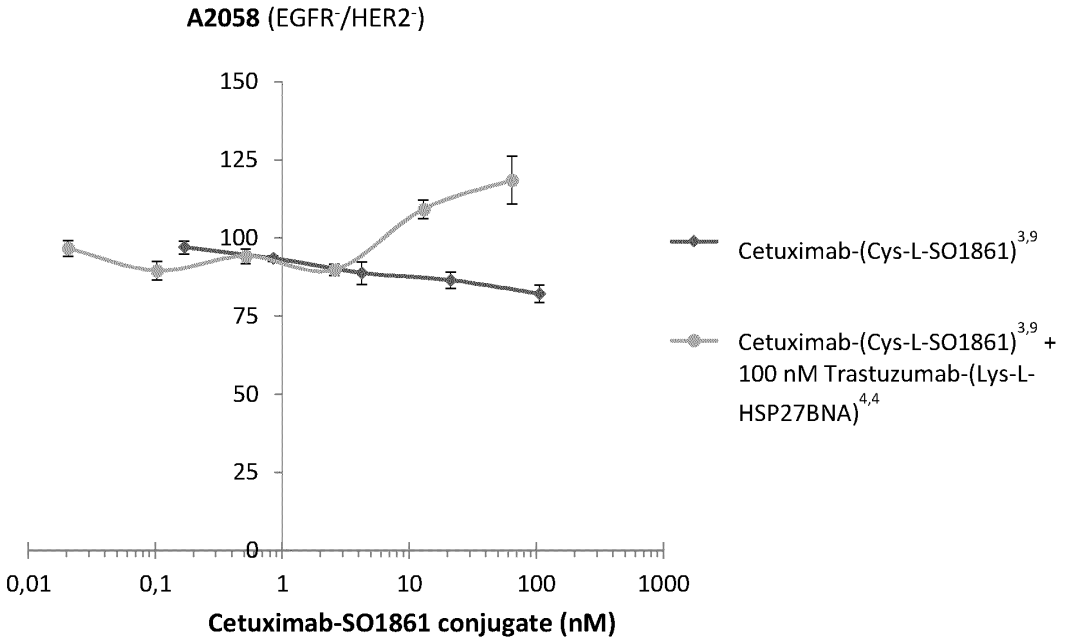
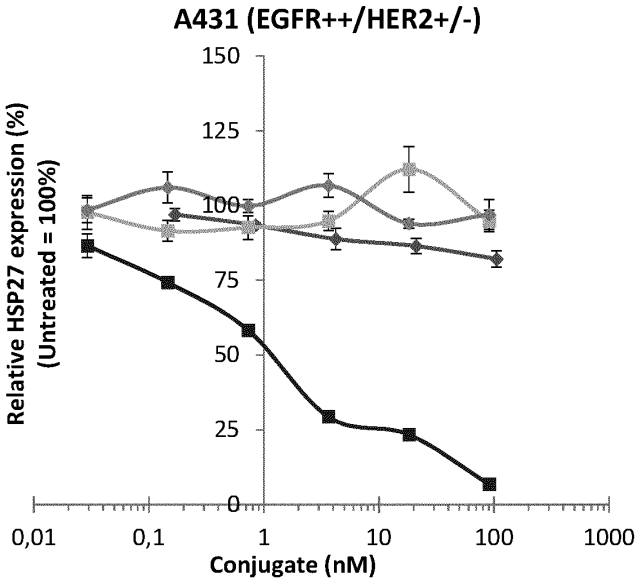


Figure 10-6

C



D

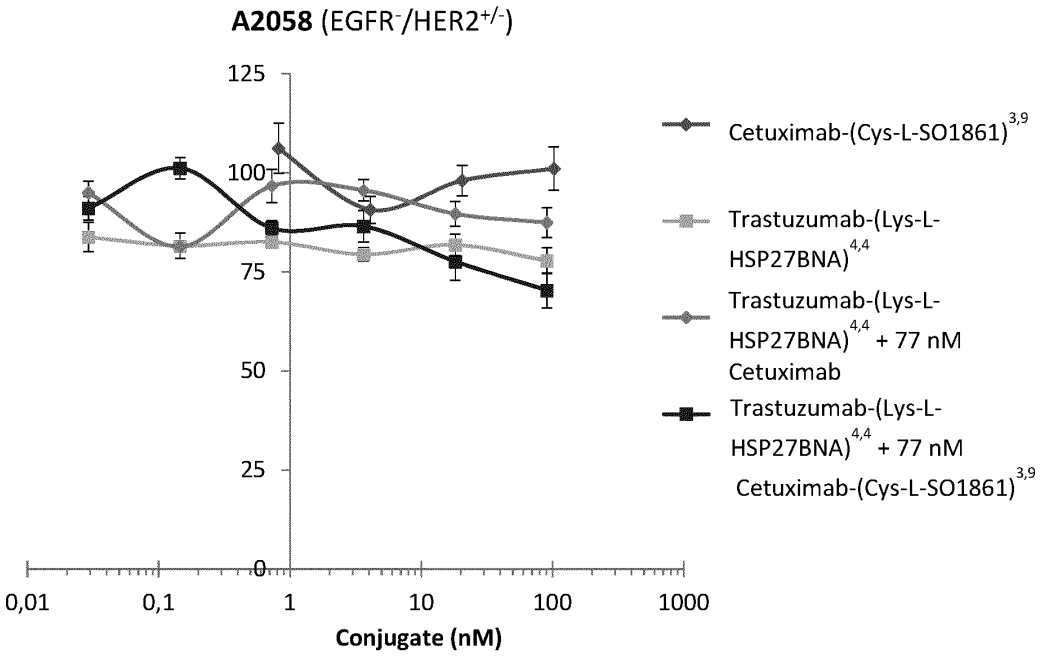
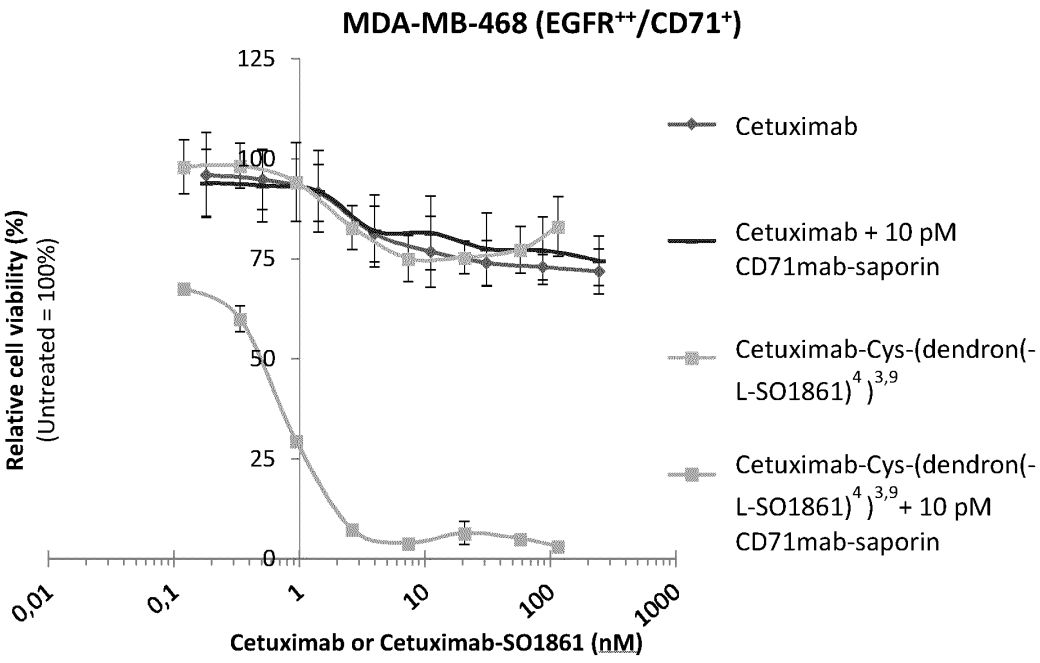


Figure 11-6

A



B

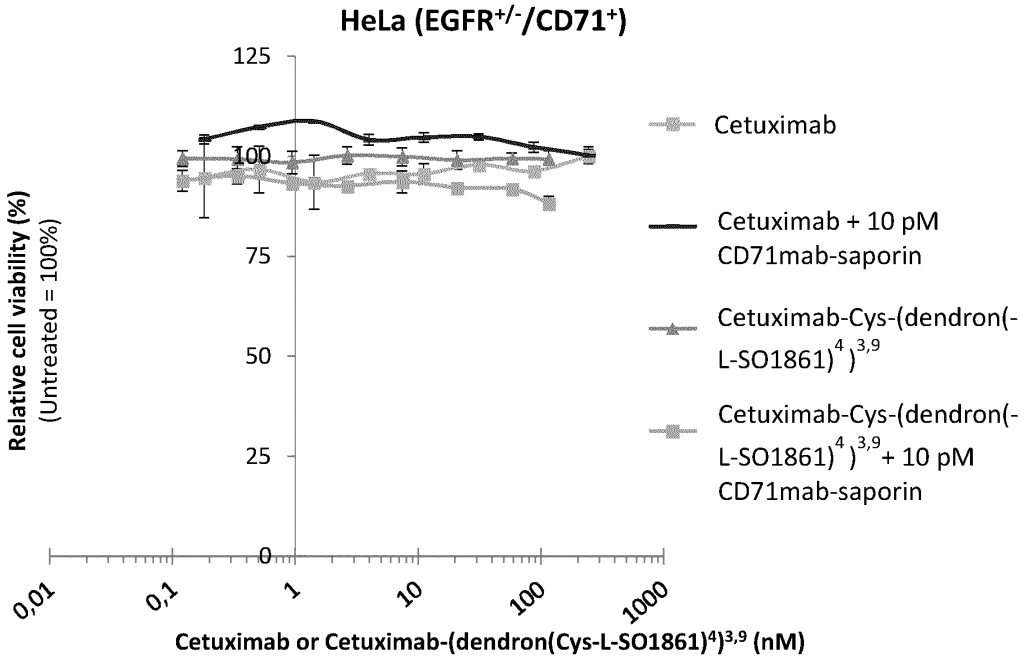
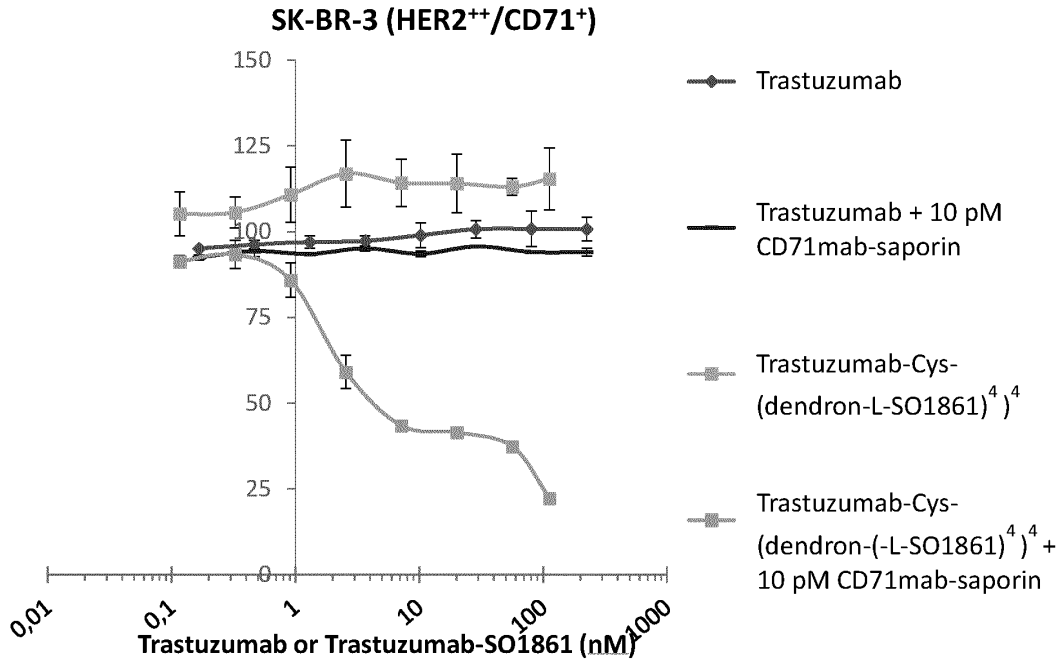


Figure 11-6

C



D

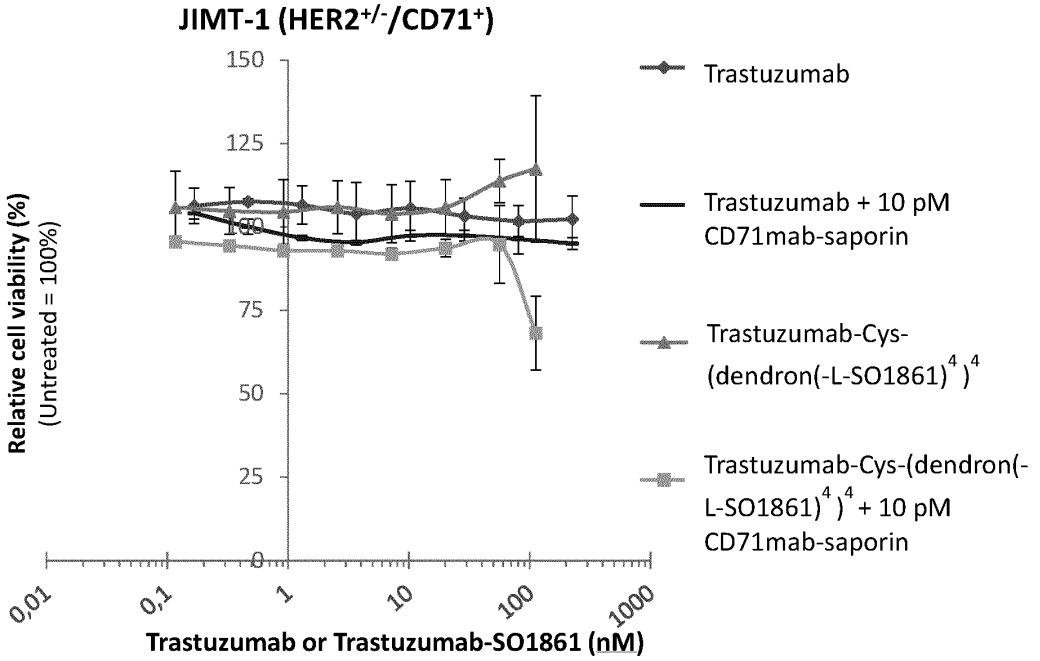


Figure 12-6

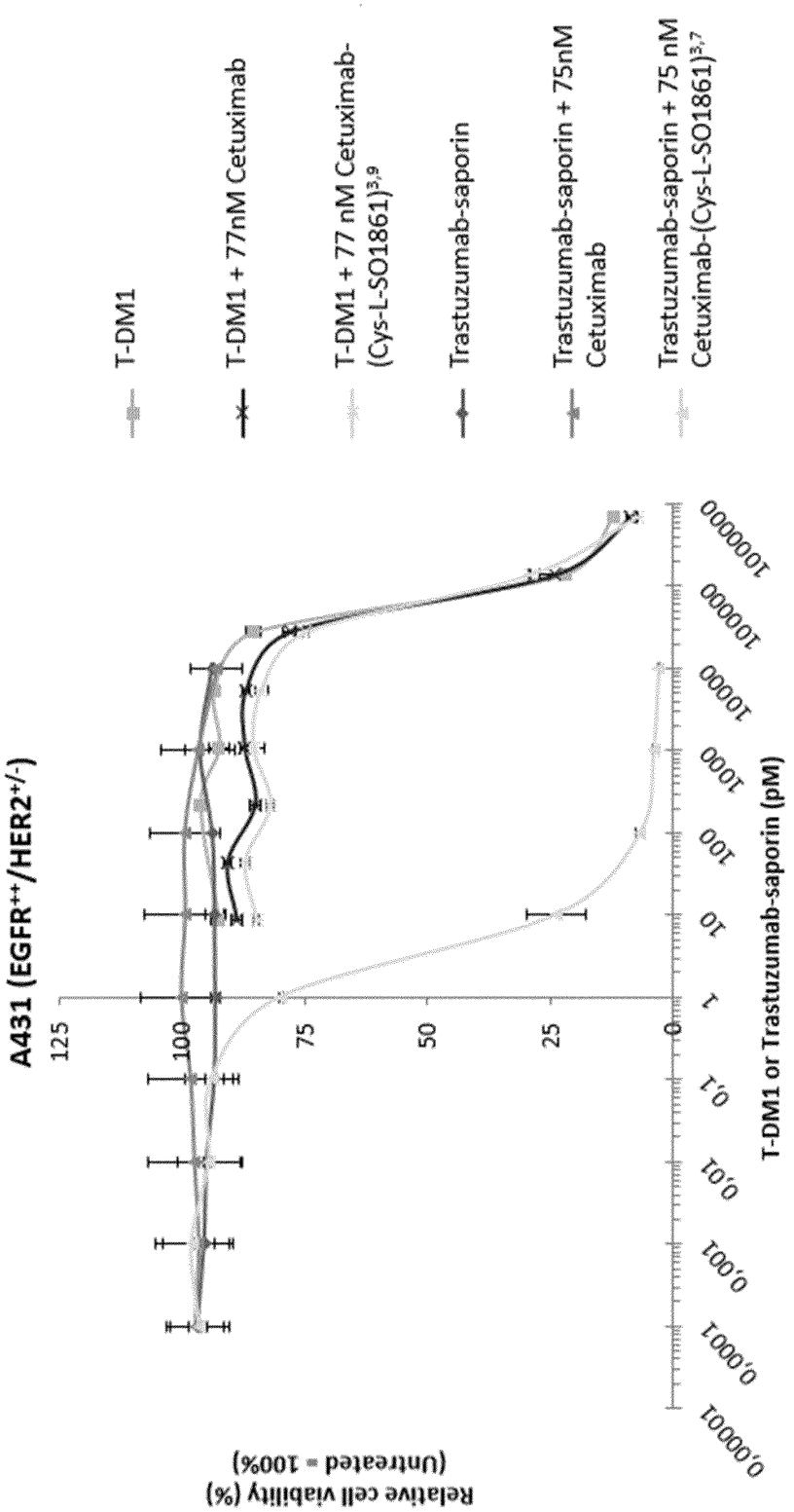
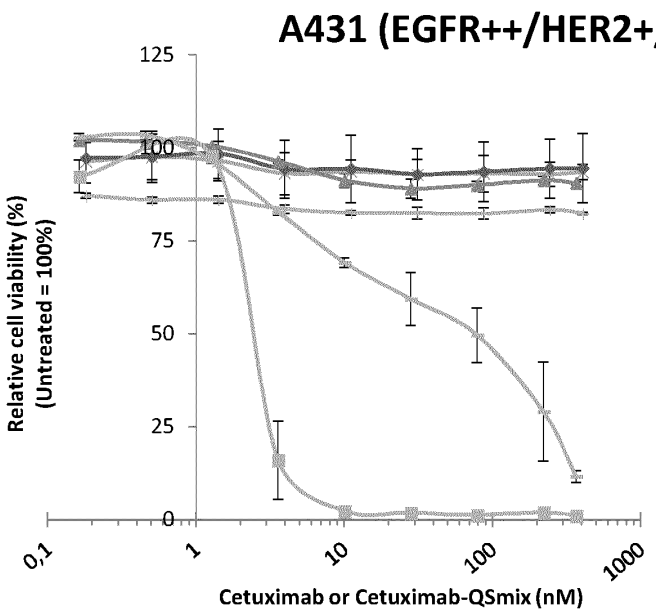

T-DM1
T-DM1 + 77nM Cetuximab
T-DM1 + 77 nM Cetuximab-(Cys-L-SO1861)3,9
Trastuzumab-saporin
Trastuzumab-saporin + 75nM Cetuximab
Trastuzumab-saporin + 75 nM Cetuximab-(Cys-L-SO1861)3,7
A431 (EGFR++/HER2+/-)
Relative cell viability (%) (Untreated = 100%)
125
100
75
50
25
0
T-DM1 or Trastuzumab-saporin (pM)
0,00001
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
100000
1000000

Figure 13-6

A



B

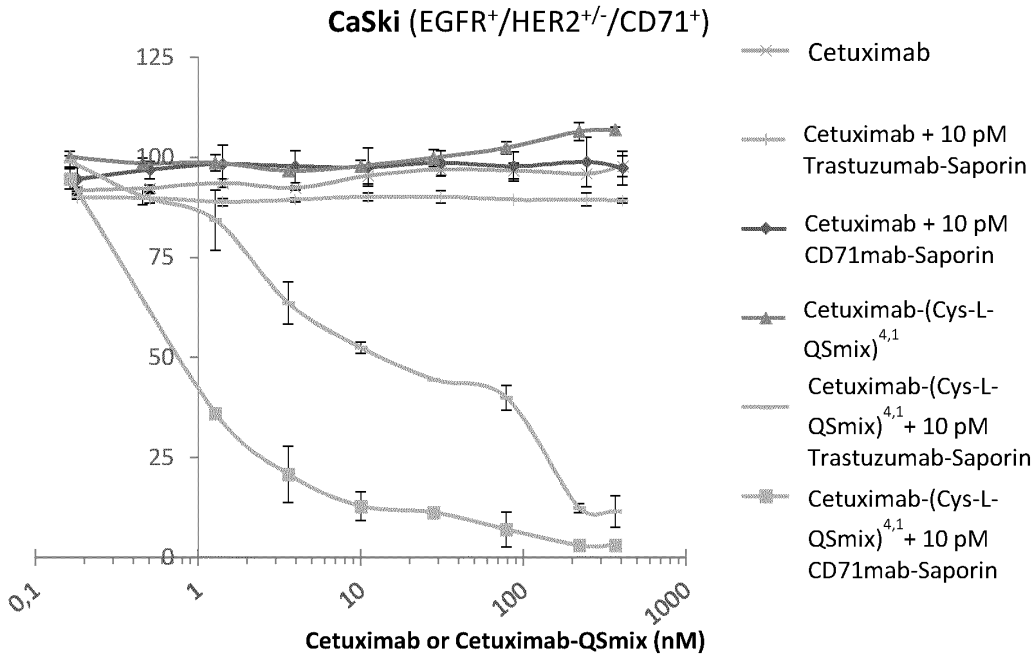


Figure 13-6

C

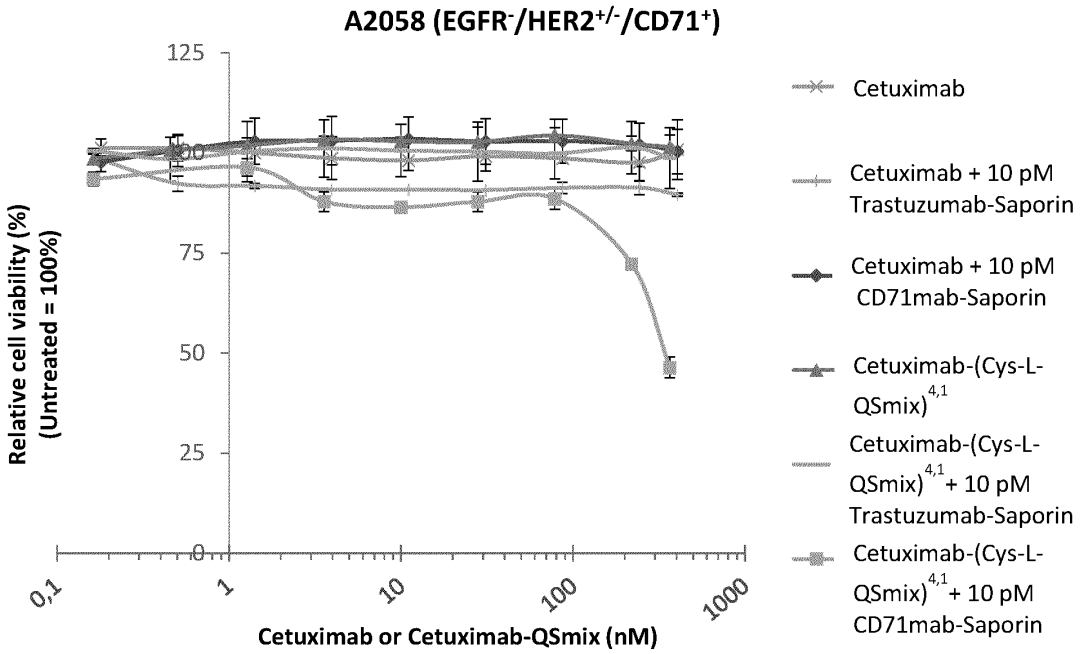


Figure 14-6

A

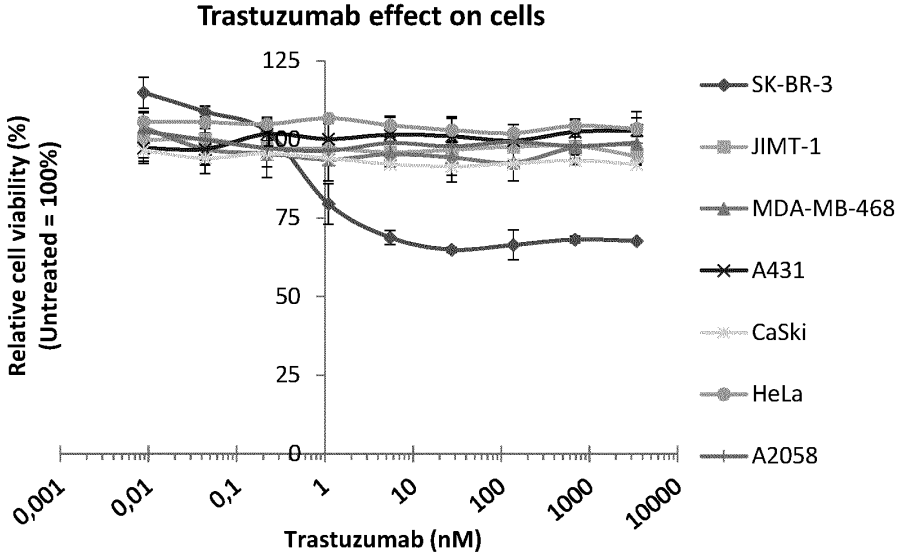
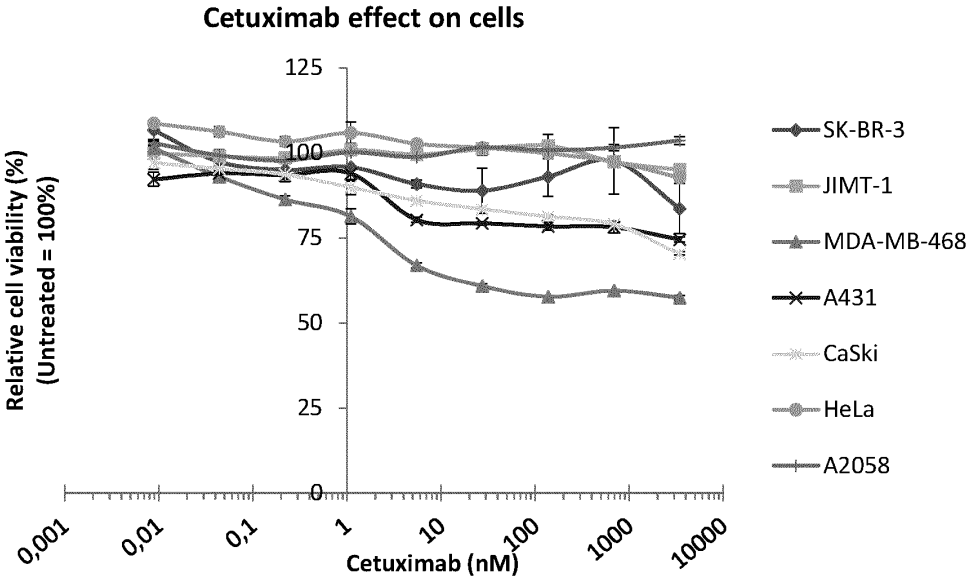


Figure 14-6

B



C

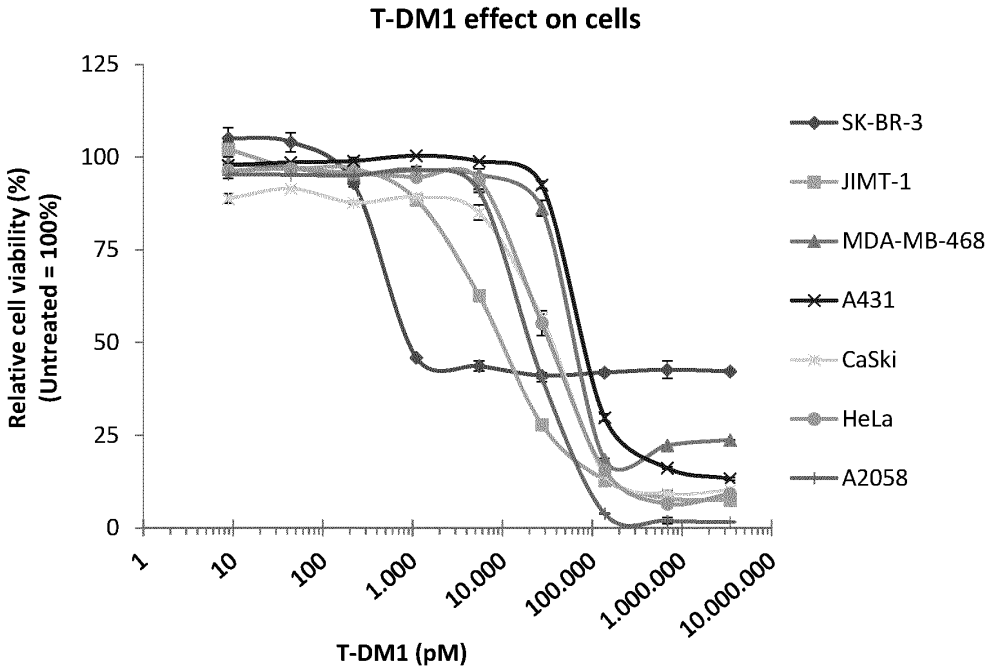


Figure 14-6

D

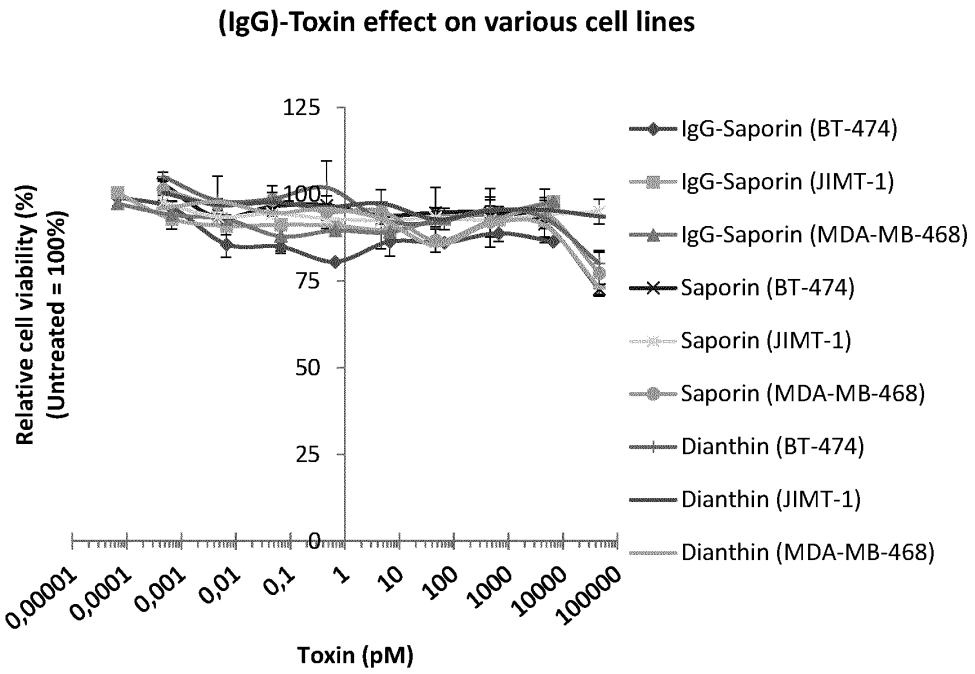

(IgG)-Toxin effect on various cell lines
Relative cell viability (%)
(Untreated = 100%)
125
100
75
50
25
0
0,00001
0,0001
0,001
0,01
0,1
1
10
100
1000
10000
100000
Toxin (pM)
IgG-Saporin (BT-474)
IgG-Saporin (JIMT-1)
IgG-Saporin (MDA-MB-468)
Saporin (BT-474)
Saporin (JIMT-1)
Saporin (MDA-MB-468)
Dianthin (BT-474)
Dianthin (JIMT-1)
Dianthin (MDA-MB-468)

Figure 15-6

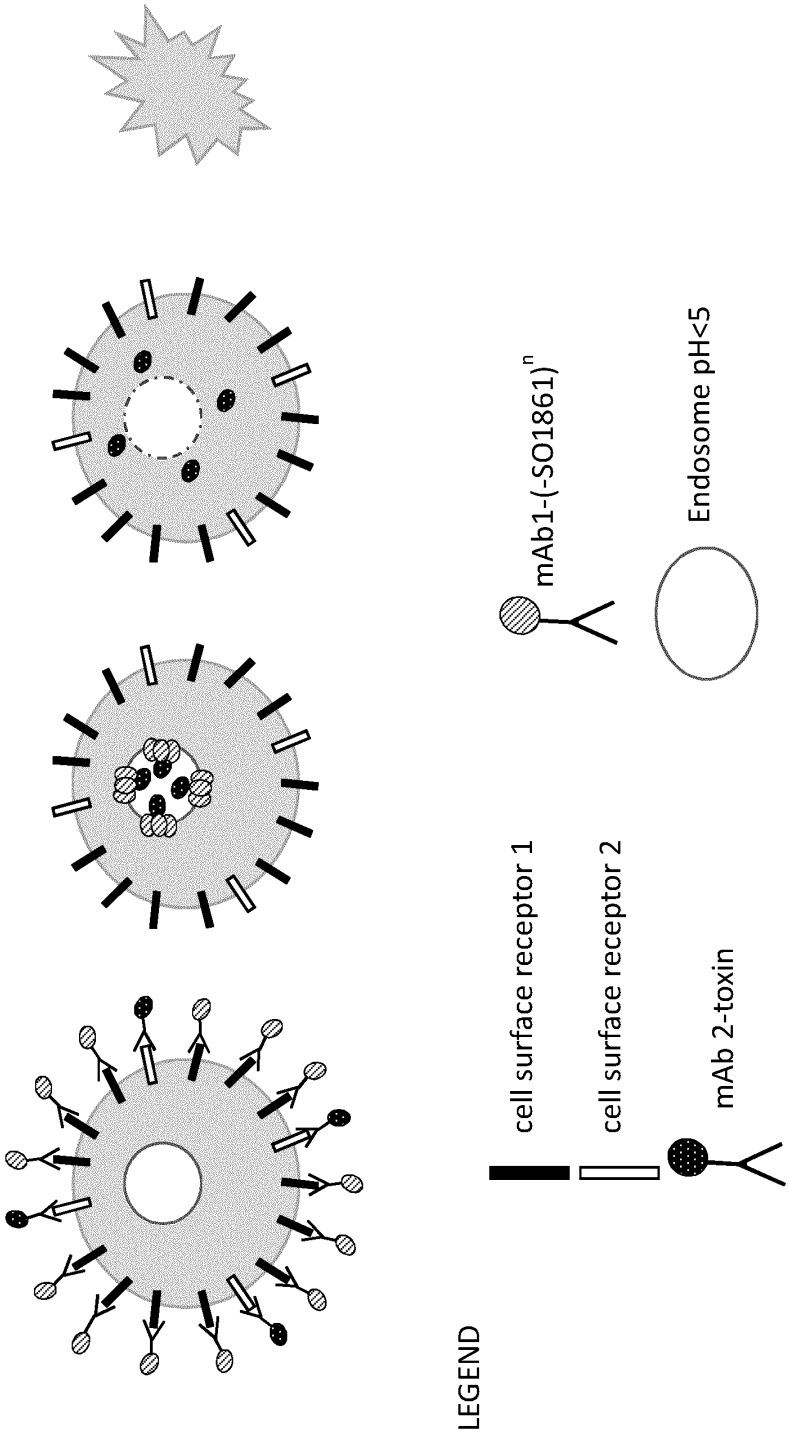

mAb1-(-SO1861)n
Endosome pH<5
cell surface receptor 1
cell surface receptor 2
mAb 2-toxin
LEGEND

Figure 16-6

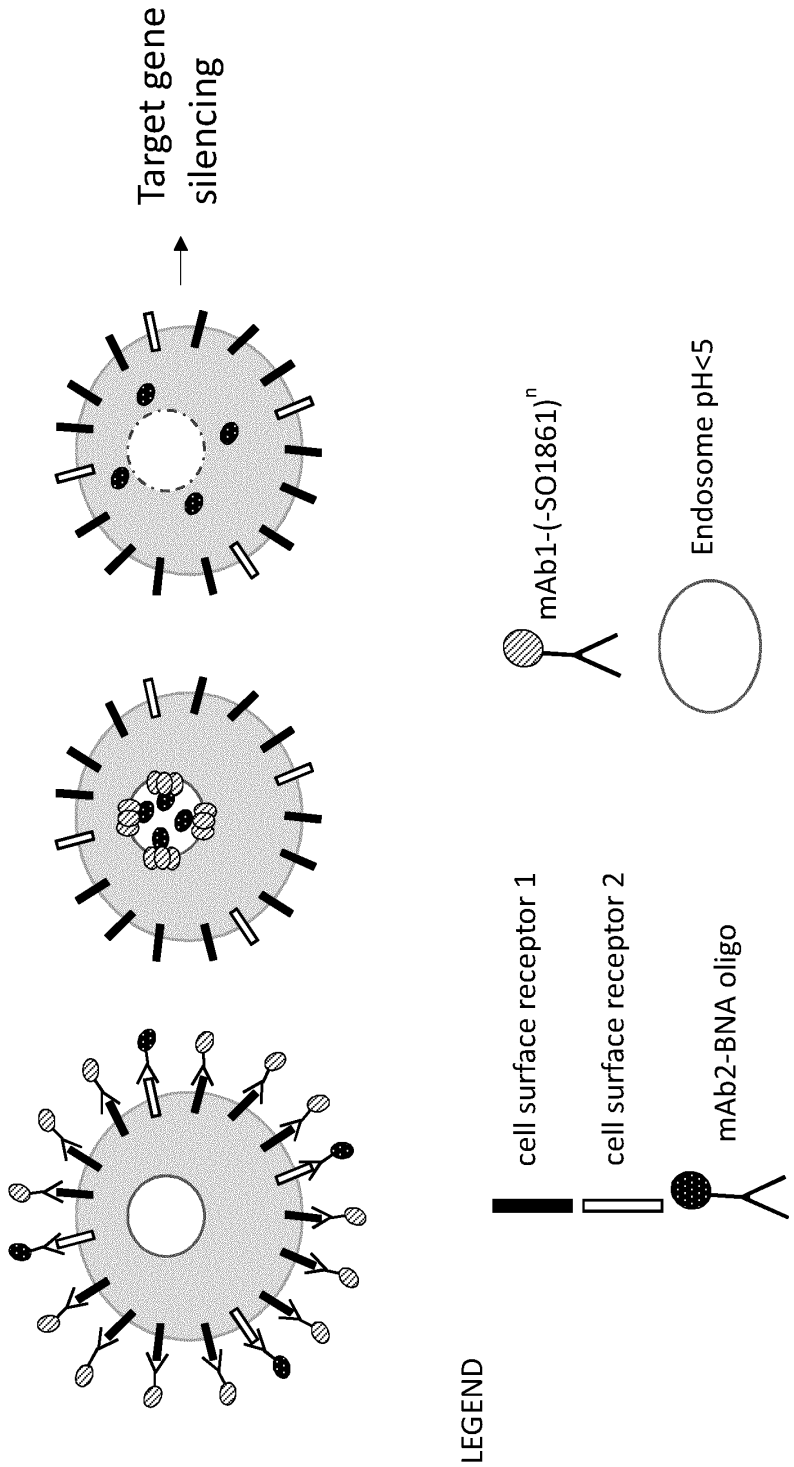

Target gene silencing
mAb1-(-SO1861)n
Endosome pH<5
cell surface receptor 1
cell surface receptor 2
mAb2-BNA oligo
LEGEND

Figure 17-6

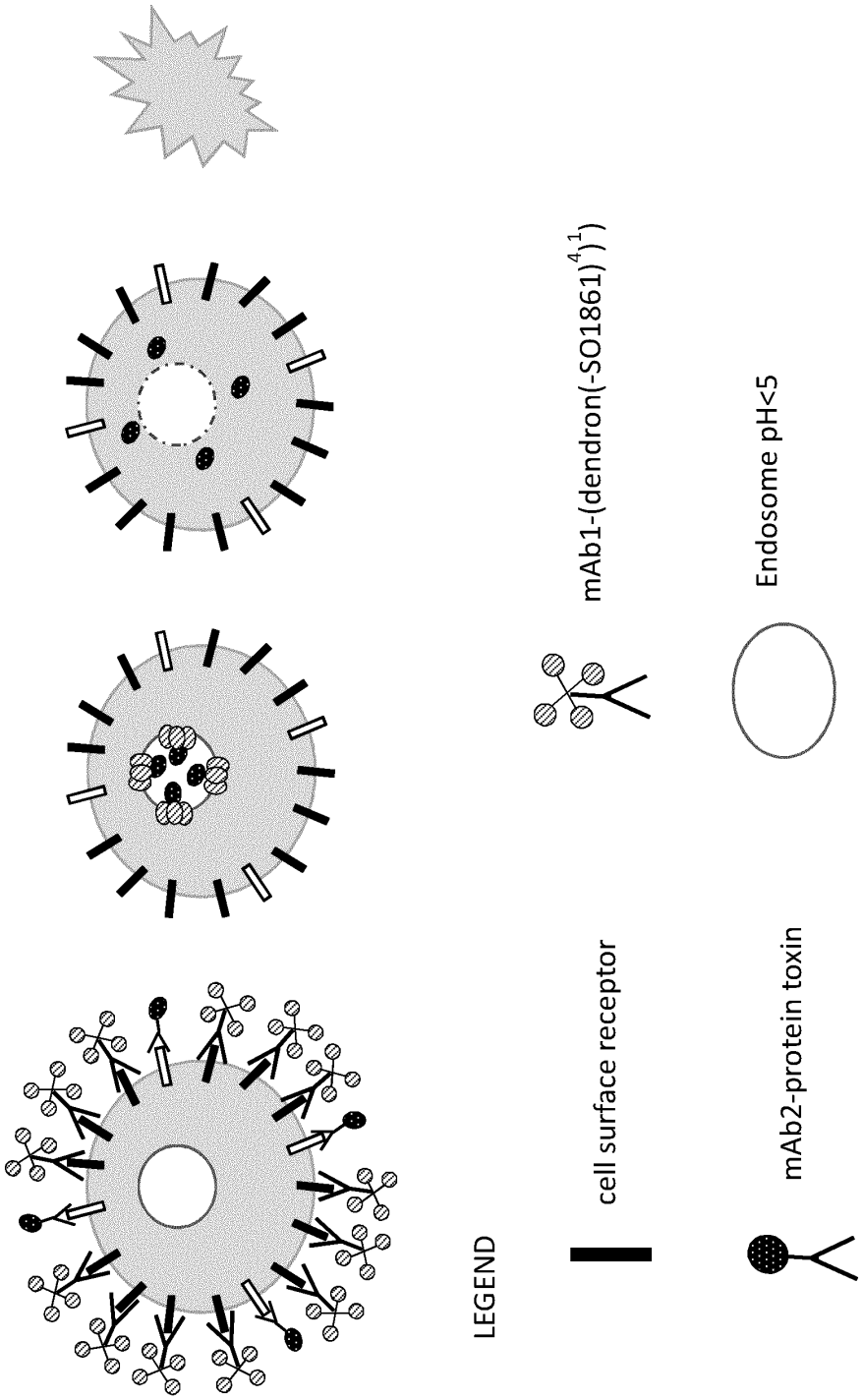
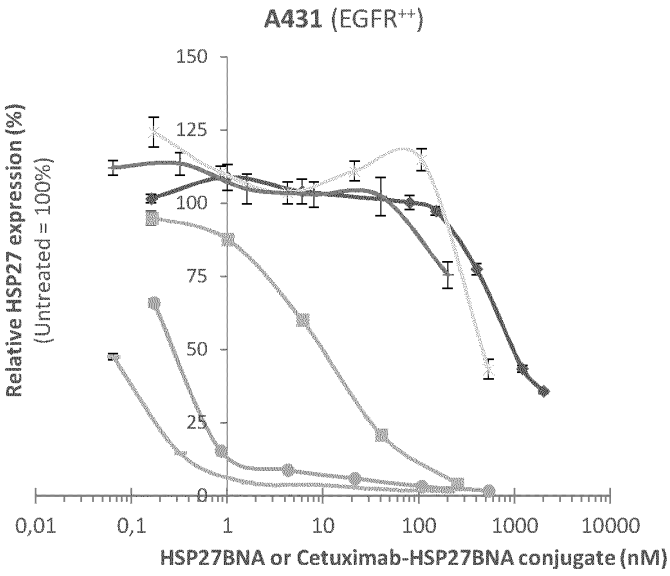

LEGEND
cell surface receptor
mAb2-protein toxin
mAb1-(dendron(-SO1861)^{4})^{1})
Endosome pH<5

Figure 1-7

A.


A431 (EGFR++)
Relative HSP27 expression (%)
(Untreated = 100%)
150
125
100
75
50
25
0
0,01
0,1
1
10
100
1000
10000
HSP27BNA or Cetuximab-HSP27BNA conjugate (nM)

B.

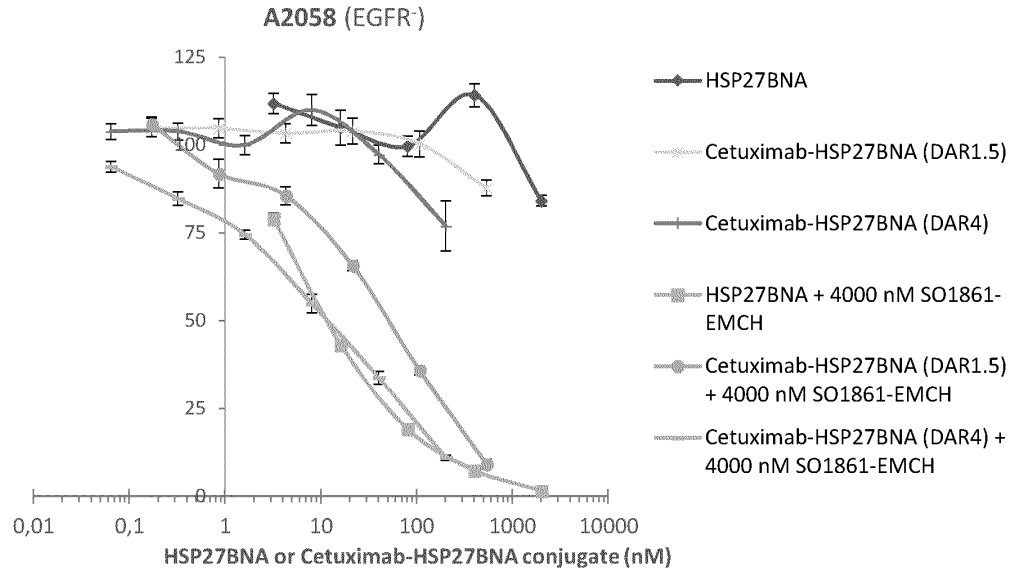
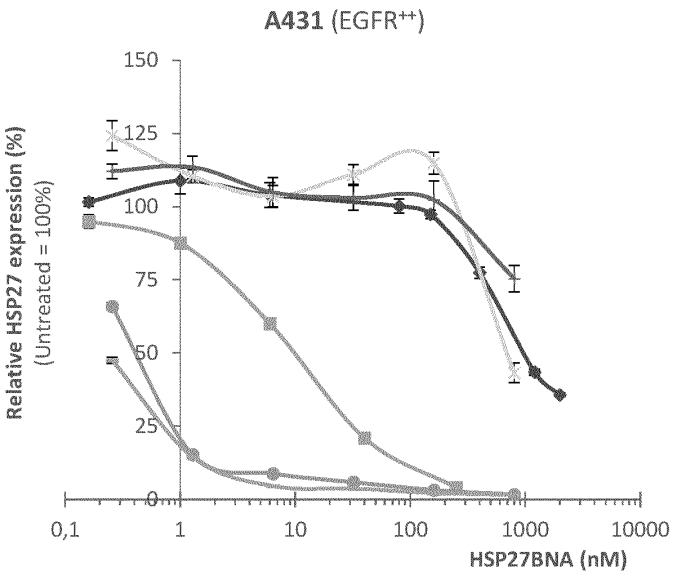
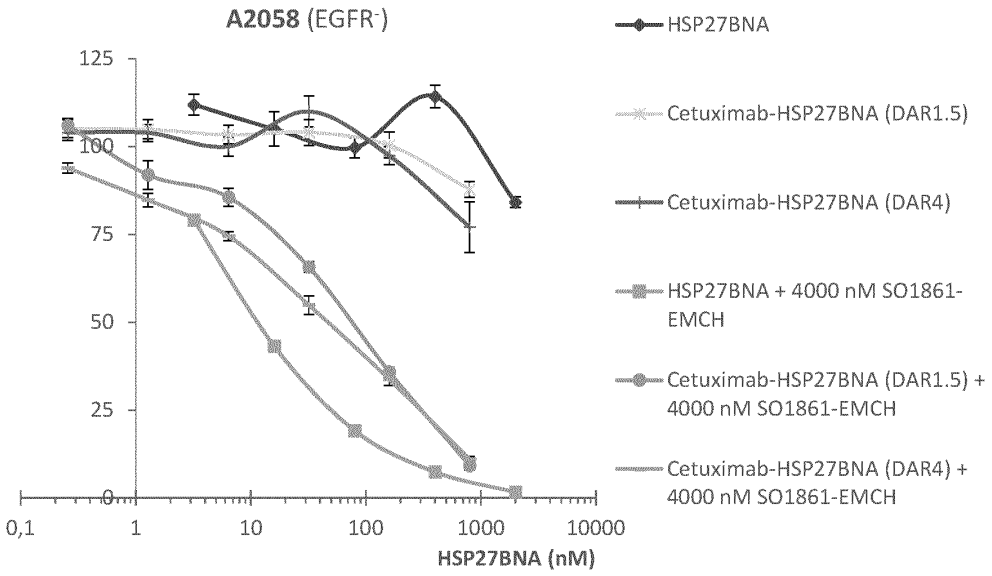

A2058 (EGFR-)
125
100
75
50
25
0
0,01
0,1
1
10
100
1000
10000
HSP27BNA or Cetuximab-HSP27BNA conjugate (nM)
HSP27BNA
Cetuximab-HSP27BNA (DAR1.5)
Cetuximab-HSP27BNA (DAR4)
HSP27BNA + 4000 nM SO1861-EMCH
Cetuximab-HSP27BNA (DAR1.5) + 4000 nM SO1861-EMCH
Cetuximab-HSP27BNA (DAR4) + 4000 nM SO1861-EMCH

Figure 1-7

C


A431 (EGFR++)
Relative HSP27 expression (%)
(Untreated = 100%)
150
125
100
75
50
25
0
0,1
1
10
100
1000
10000
HSP27BNA (nM)

D


A2058 (EGFR-)
125
100
75
50
25
0
0,1
1
10
100
1000
10000
HSP27BNA (nM)
HSP27BNA
Cetuximab-HSP27BNA (DAR1.5)
Cetuximab-HSP27BNA (DAR4)
HSP27BNA + 4000 nM SO1861-EMCH
Cetuximab-HSP27BNA (DAR1.5) + 4000 nM SO1861-EMCH
Cetuximab-HSP27BNA (DAR4) + 4000 nM SO1861-EMCH