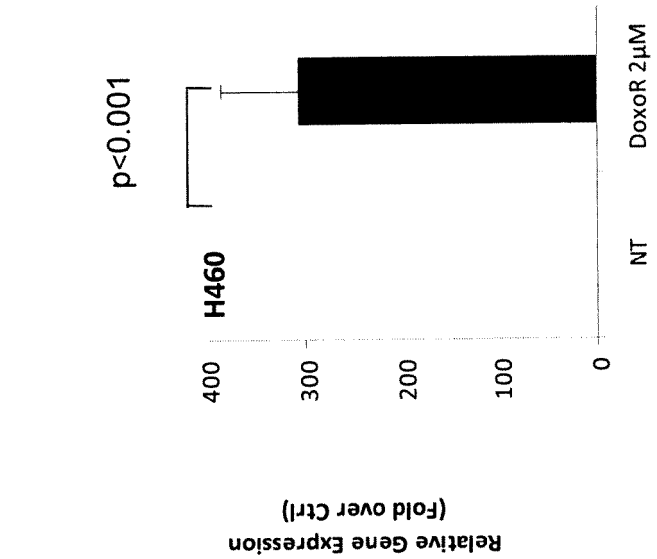

H460
p<0.001
400
300
200
100
0
NT
DoxoR 2µM
Relative Gene Expression
(Fold over Ctrl)

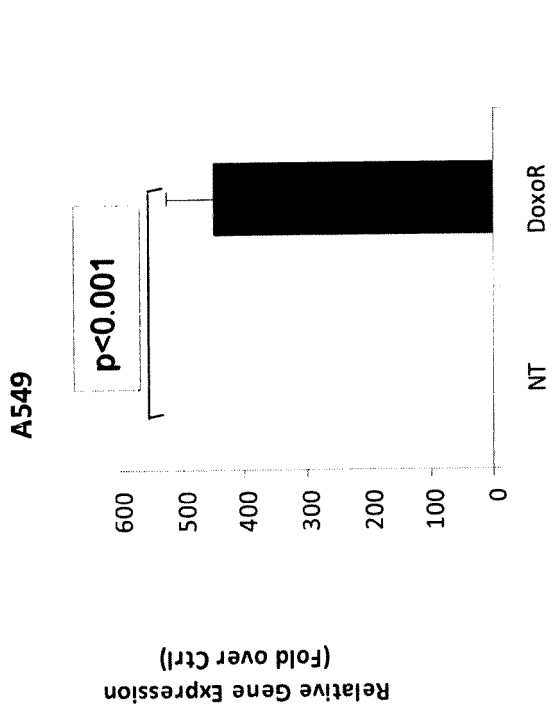

A549
p<0.001
600
500
400
300
200
100
0
NT
DoxoR
Relative Gene Expression
(Fold over Ctrl)

Fig.1

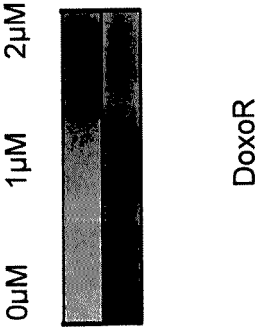

0µM
1µM
2µM
DoxoR
Netrin-1
β-Actin

Fig. 2

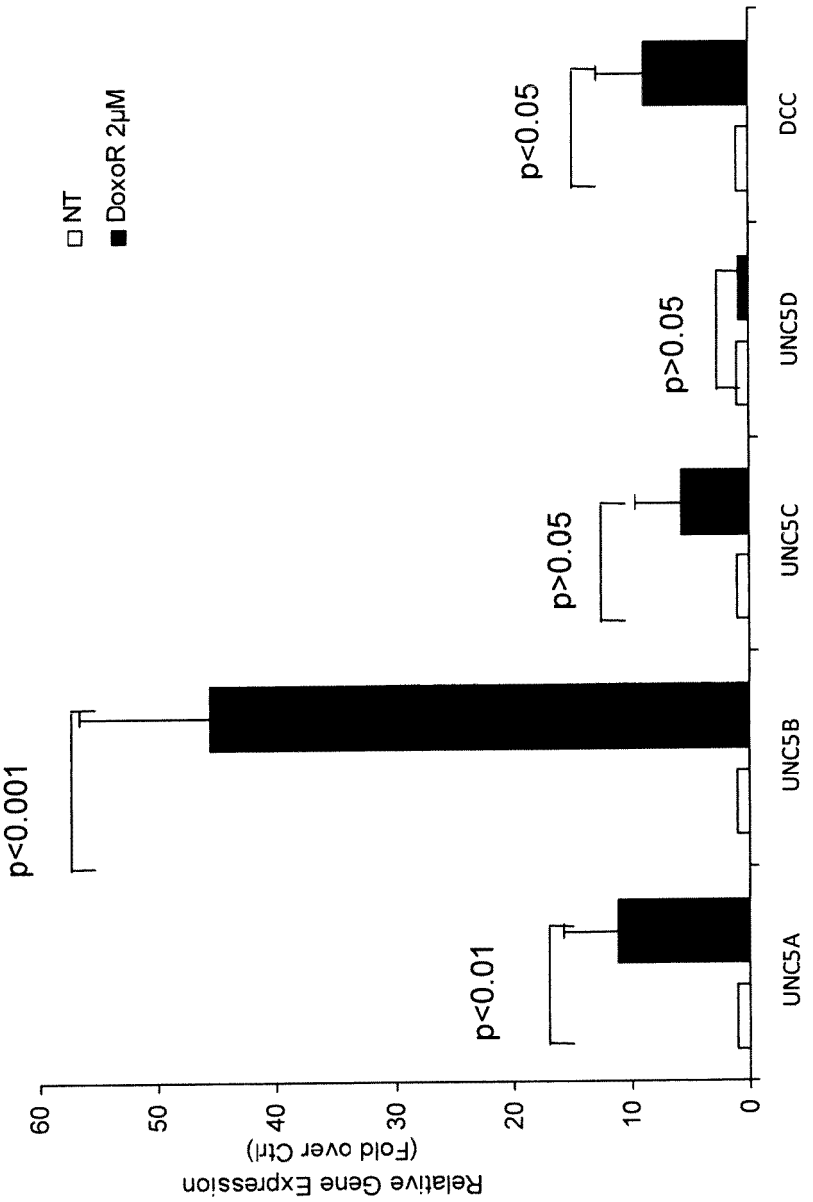

NT
DoxoR 2µM
Relative Gene Expression
(Fold over Ctrl)
0
10
20
30
40
50
60
p<0.001
p<0.01
p>0.05
p>0.05
p<0.05
UNC5A
UNC5B
UNC5C
UNC5D
DCC

Fig. 3

Fig. 4

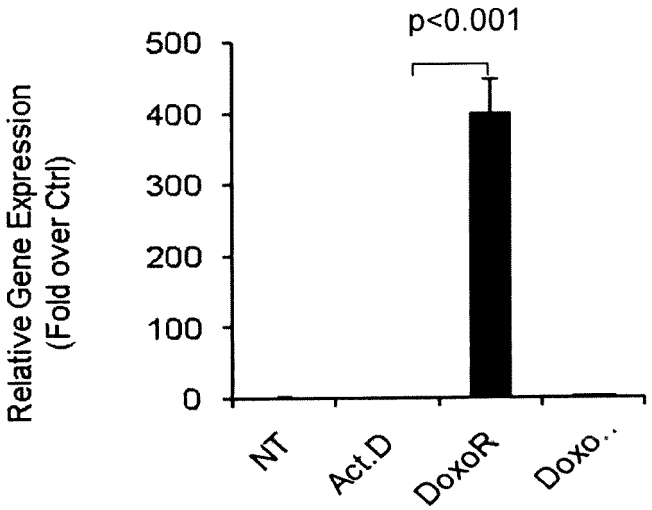
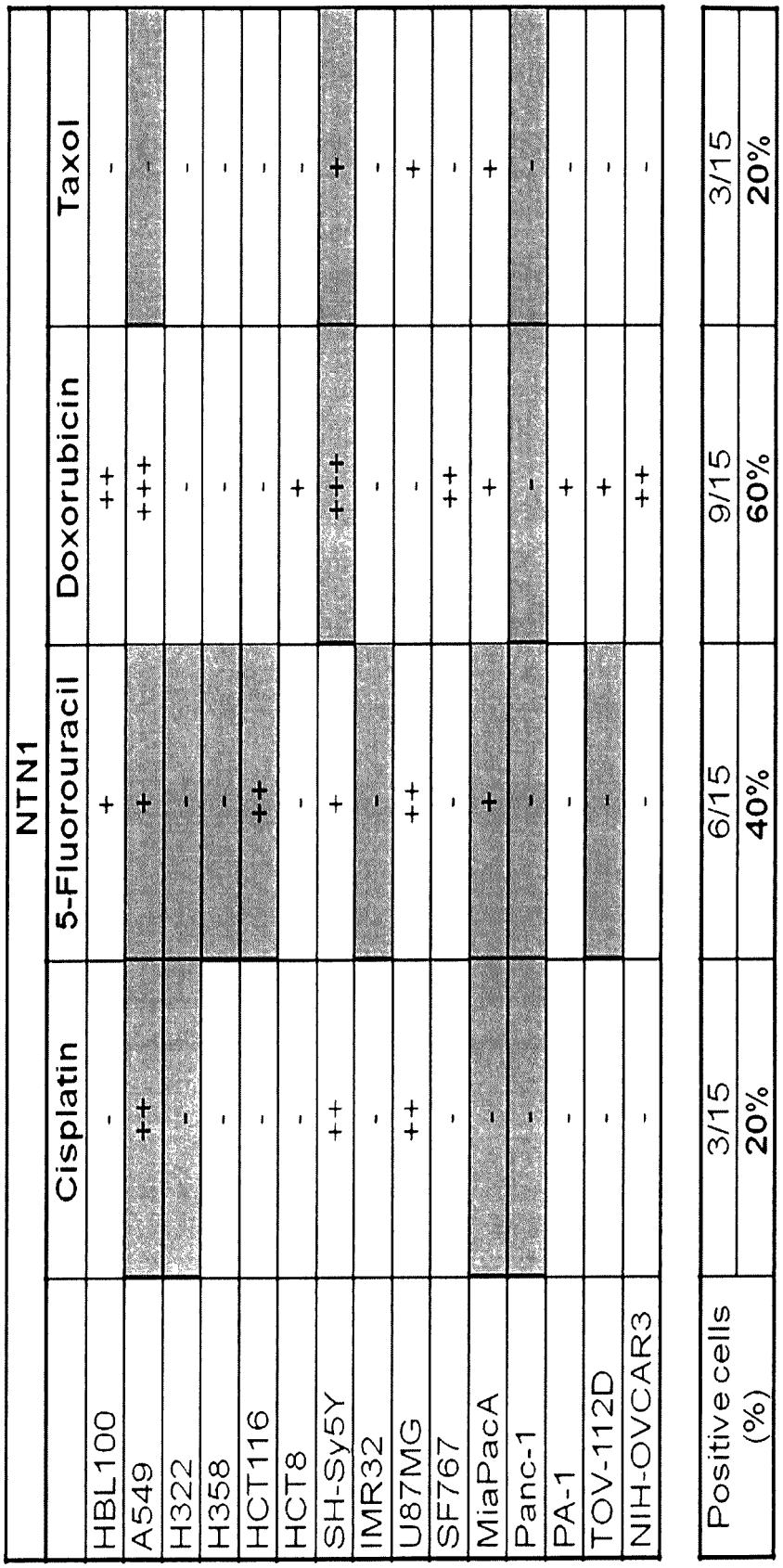
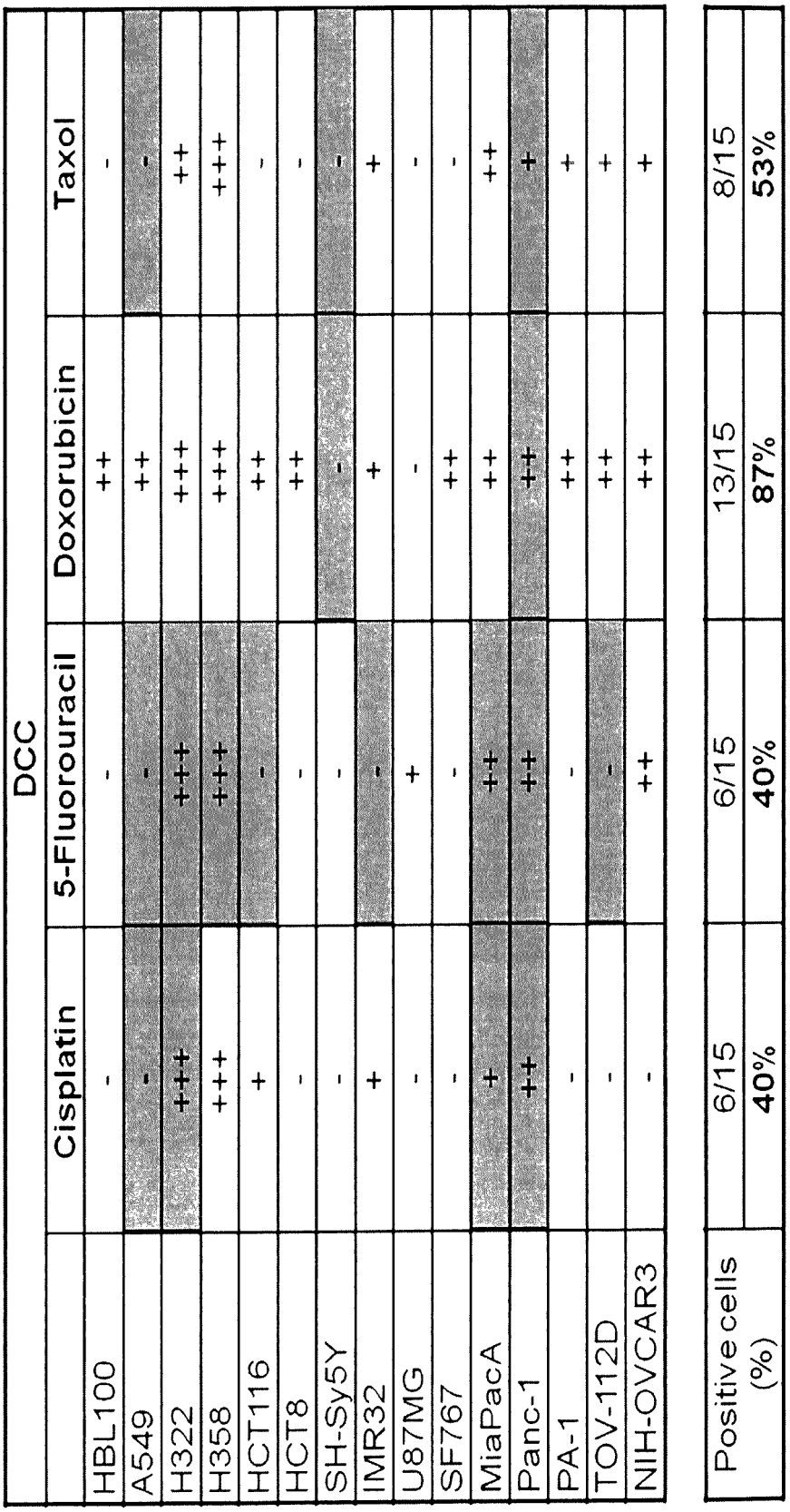

p<0.001
Relative Gene Expression
(Fold over Ctrl)
500
400
300
200
100
0
NT
Act.D
DoxoR
Doxo..

Fig. 5



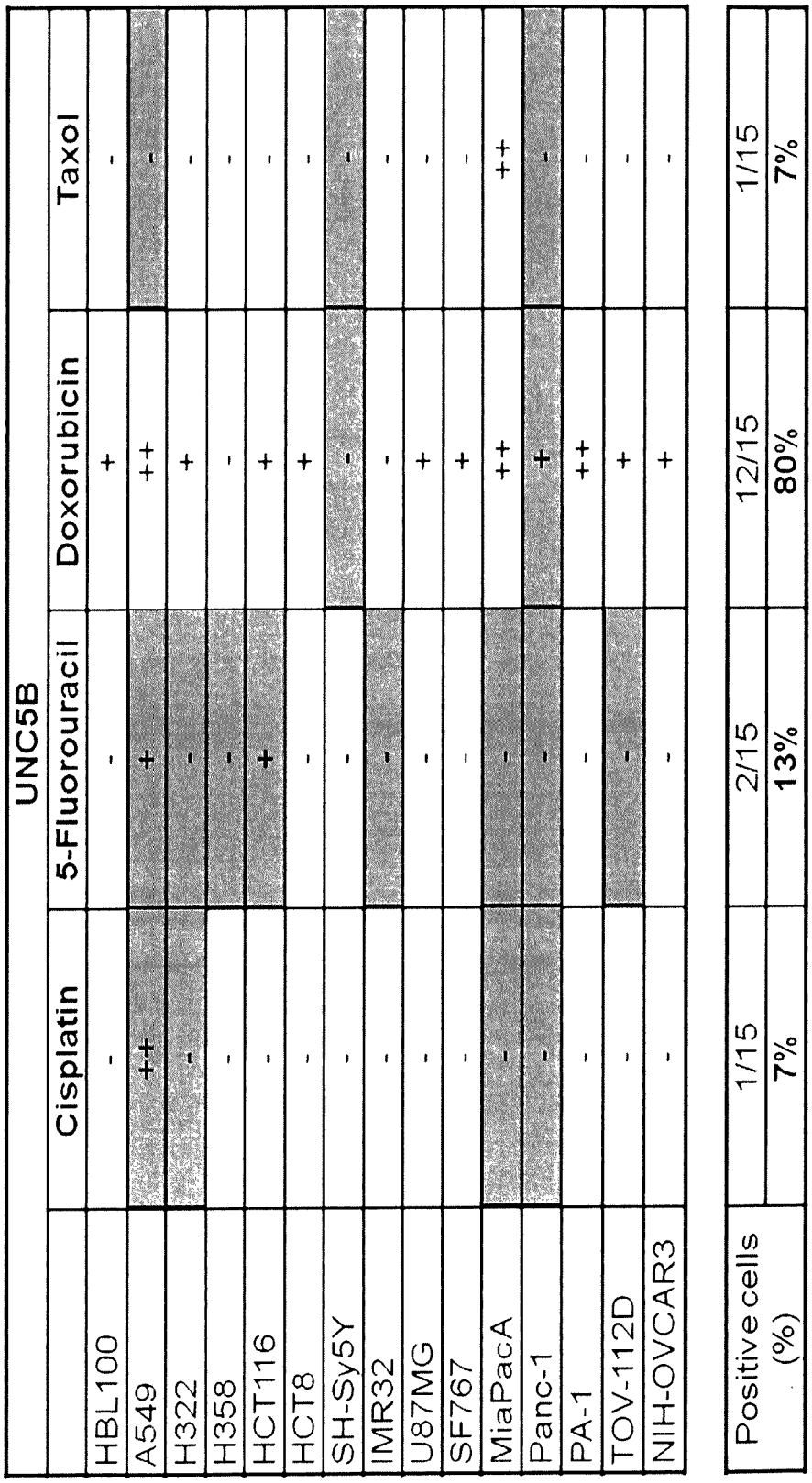
NTN1	Cisplatin	5-Fluorouracil	Doxorubicin	Taxol
HBL100	-	+	++	-
A549	++	+	+++	-
H322	-	-	-	-
H358	-	-	-	-
HCT116	-	++	-	-
HCT8	-	-	+	-
SH-Sy5Y	++	+	+++	+
IMR32	-	-	-	-
U87MG	++	++	-	+
SF767	-	-	++	-
MiaPacA	-	+	+	+
Panc-1	-	-	-	-
PA-1	-	-	+	-
TOV-112D	-	-	+	-
NIH-OVCAR3	-	-	++	-
Positive cells	3/15	6/15	9/15	3/15
(%)	20%	40%	60%	20%

Fig. 6



DCC	Cisplatin	5-Fluorouracil	Doxorubicin	Taxol
HBL100	-	-	++	-
A549	-	-	++	-
H322	+++	+++	+++	++
H358	+++	+++	+++	+++
HCT116	+	-	++	-
HCT8	-	-	++	-
SH-Sy5Y	-	-	-	-
IMR32	+	-	+	+
U87MG	-	+	-	-
SF767	-	-	++	-
MiaPacA	+	++	++	++
Panc-1	++	++	++	+
PA-1	-	-	++	+
TOV-112D	-	-	++	+
NIH-OVCAR3	-	++	++	+
Positive cells	6/15	6/15	13/15	8/15
(%)	40%	40%	87%	53%

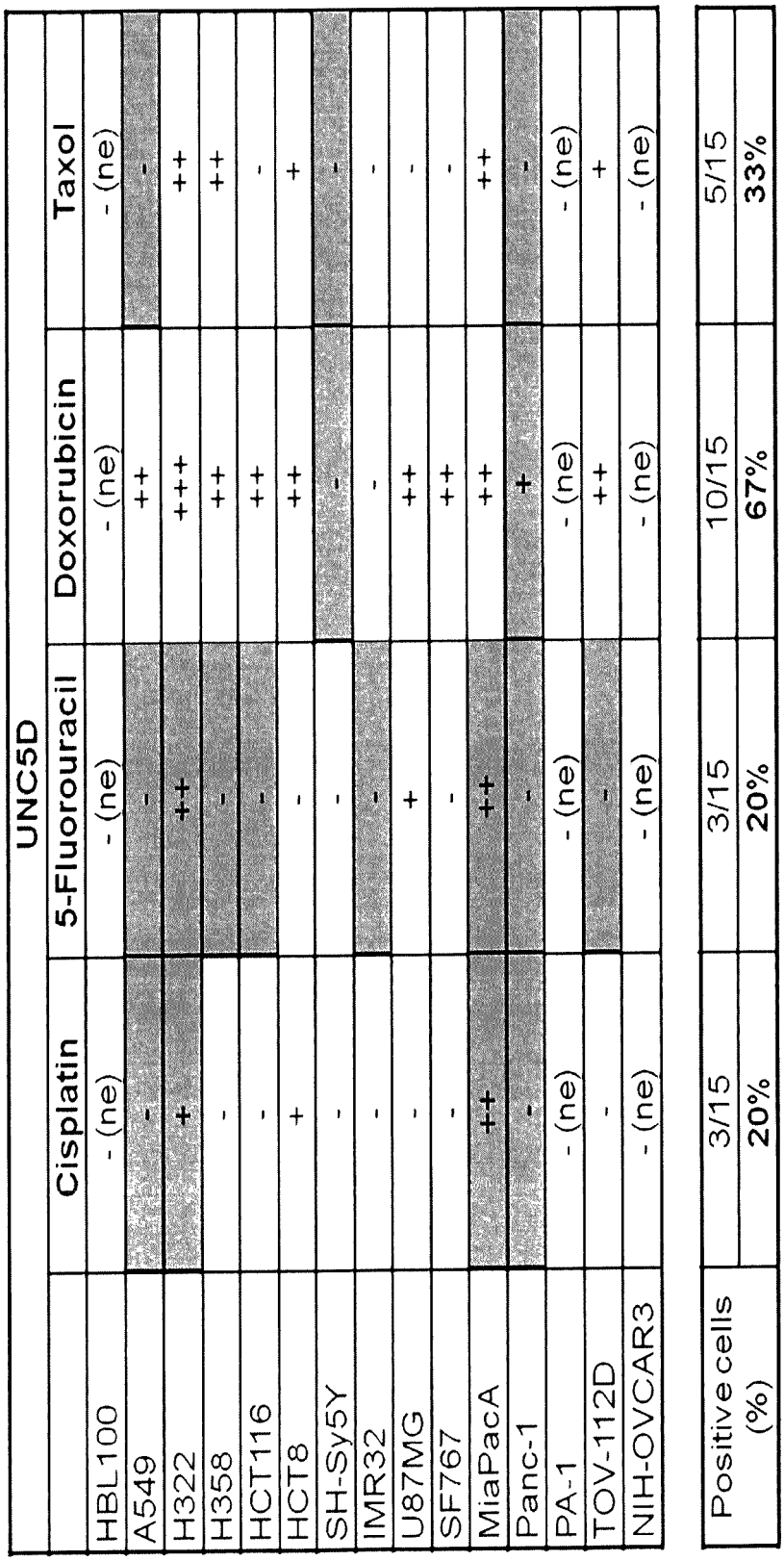
Fig. 7



UNC5B	Cisplatin	5-Fluorouracil	Doxorubicin	Taxol
HBL100	-	-	+	-
A549	++	+	++	-
H322	-	-	+	-
H358	-	-	-	-
HCT116	-	+	+	-
HCT8	-	-	+	-
SH-Sy5Y	-	-	-	-
IMR32	-	-	-	-
U87MG	-	-	+	-
SF767	-	-	+	-
MiaPacA	-	-	++	++
Panc-1	-	-	+	-
PA-1	-	-	++	-
TOV-112D	-	-	+	-
NIH-OVCAR3	-	-	+	-

Positive cells (%)	1/15	2/15	12/15	1/15
	7%	13%	80%	7%

Fig. 8



UNC5D				
	Cisplatin	5-Fluorouracil	Doxorubicin	Taxol
HBL100	- (ne)	- (ne)	- (ne)	- (ne)
A549	-	-	++	-
H322	+	++	+++	++
H358	-	-	++	++
HCT116	-	-	++	-
HCT8	+	-	++	+
SH-Sy5Y	-	-	-	-
IMR32	-	-	-	
U87MG	-	+	++	-
SF767	-	-	++	-
MiaPacA	++	++	++	++
Panc-1	-	-	+	-
PA-1	- (ne)	- (ne)	- (ne)	- (ne)
TOV-112D	-	-	++	+
NIH-OVCAR3	- (ne)	- (ne)	- (ne)	- (ne)

Positive cells (%)	3/15	3/15	10/15	5/15
	20%	20%	67%	33%

Fig. 9

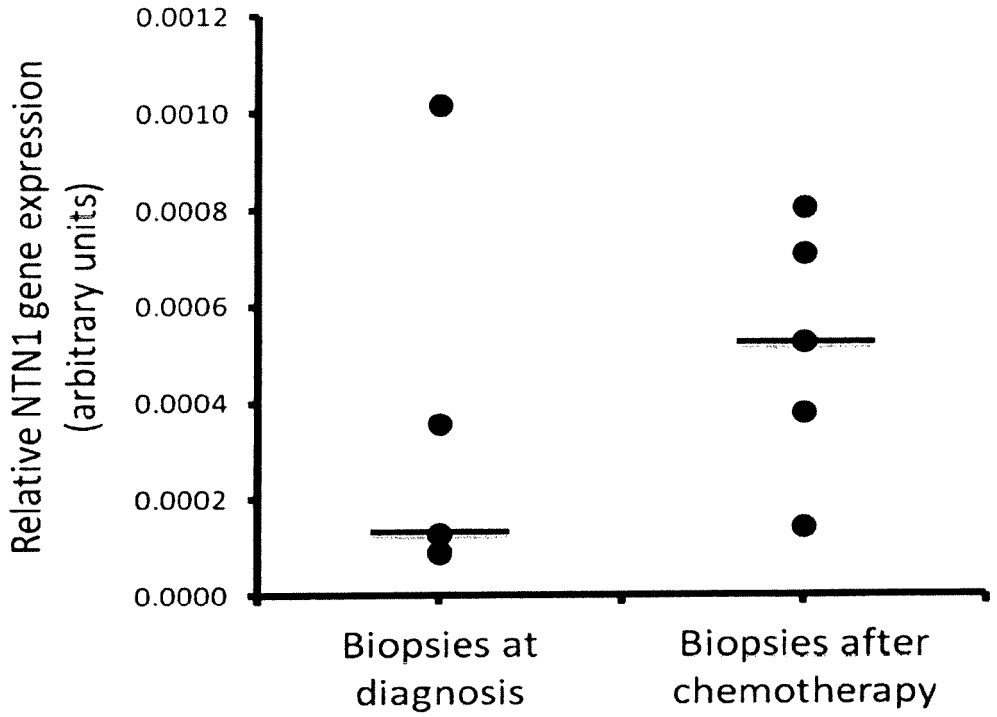

Relative NTN1 gene expression (arbitrary units)
0.0012
0.0010
0.0008
0.0006
0.0004
0.0002
0.0000
Biopsies at diagnosis
Biopsies after chemotherapy

Fig. 11

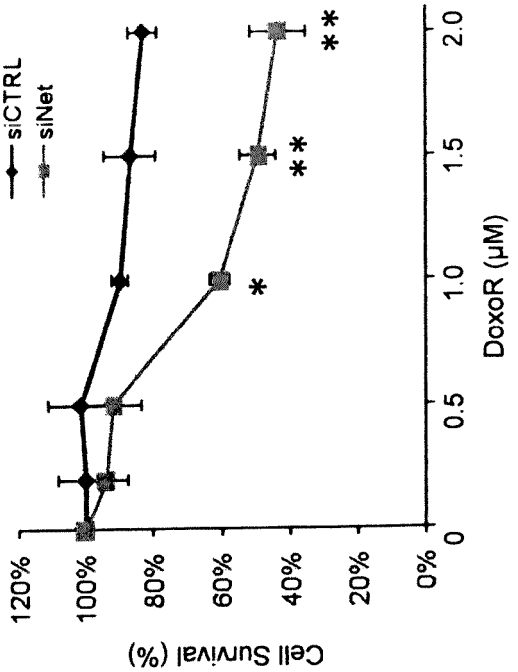

siCTRL
siNet
Cell Survival (%)
120%
100%
80%
60%
40%
20%
0%
0
0.5
1.0
1.5
2.0
DoxoR (µM)
*
**
**

Fig. 10

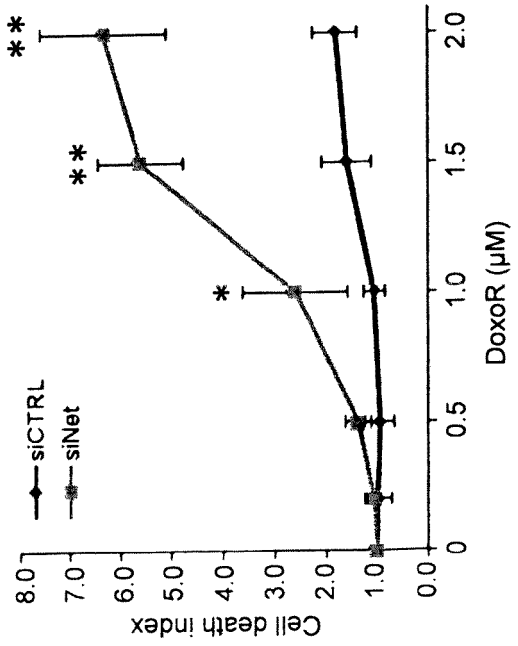

siCTRL
siNet
Cell death index
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0
0.5
1.0
1.5
2.0
DoxoR (µM)
*
**
**

Fig. 12

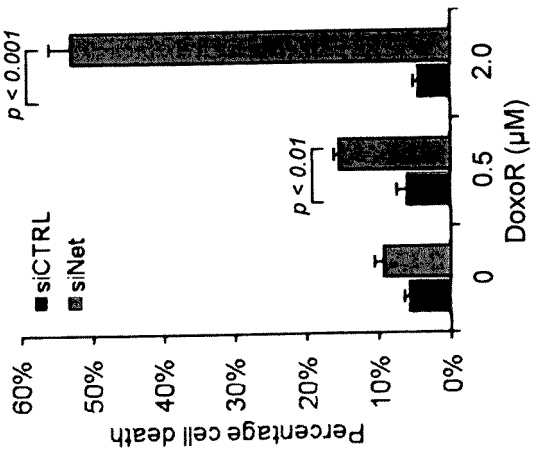


Fig.13

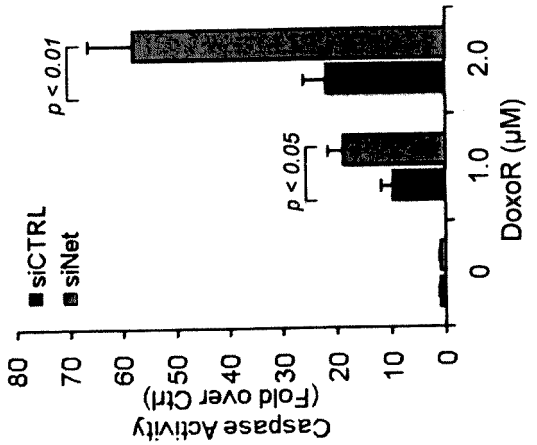
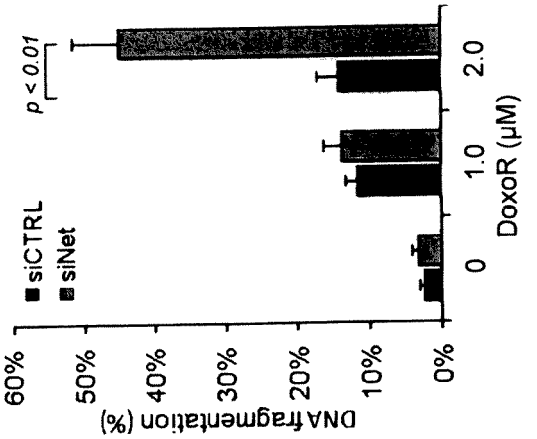


Fig.14



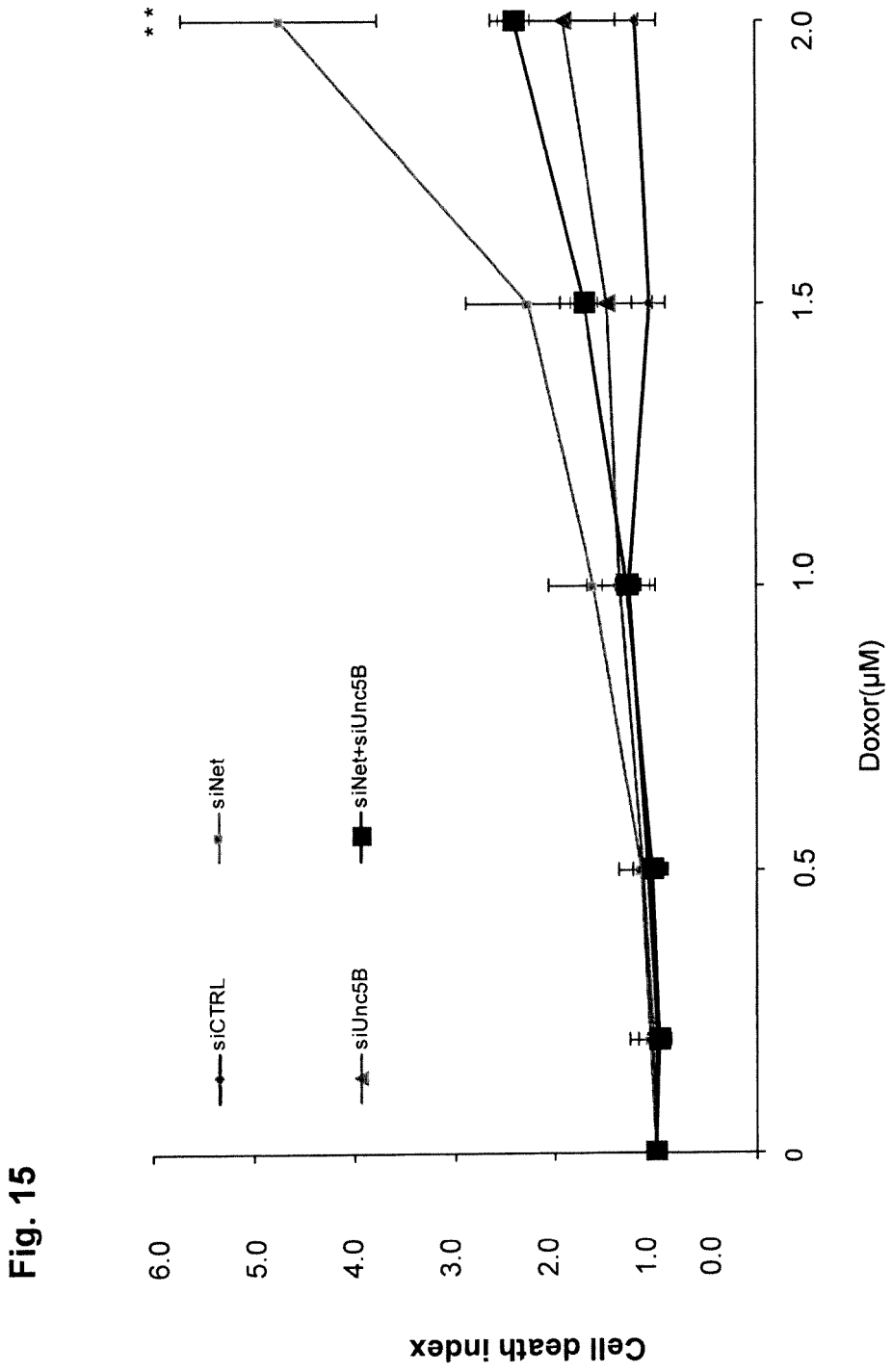

Cell death index
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0
0.5
1.0
1.5
2.0
Doxor(µM)
siCTRL
siNet
siUnc5B
siNet+siUnc5B
* *

Fig. 15

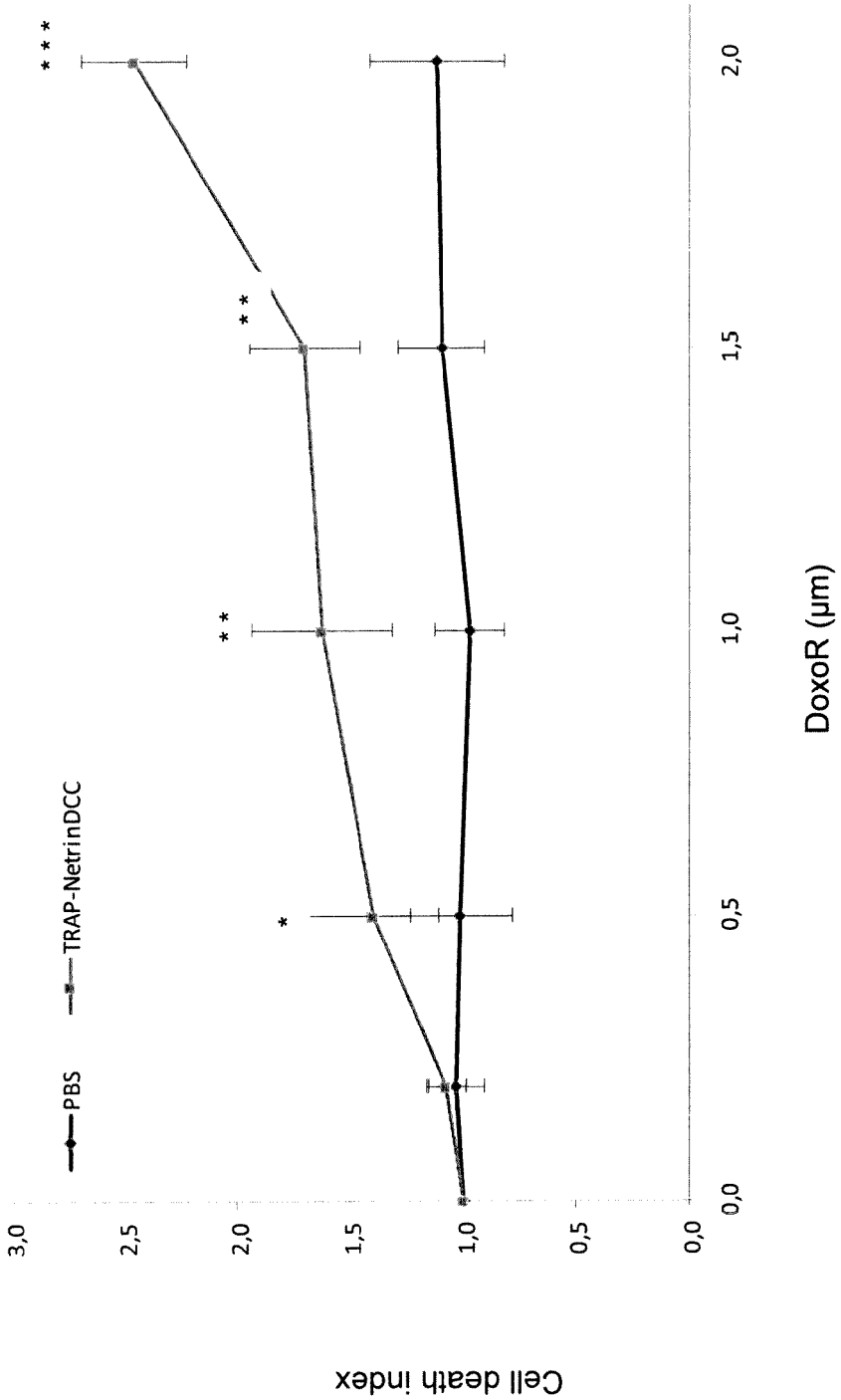

Cell death index
DoxoR (µm)
PBS
TRAP-NetrinDCC
3,0
2,5
2,0
1,5
1,0
0,5
0,0
0,0
0,5
1,0
1,5
2,0
*
**
**
***

Fig. 16

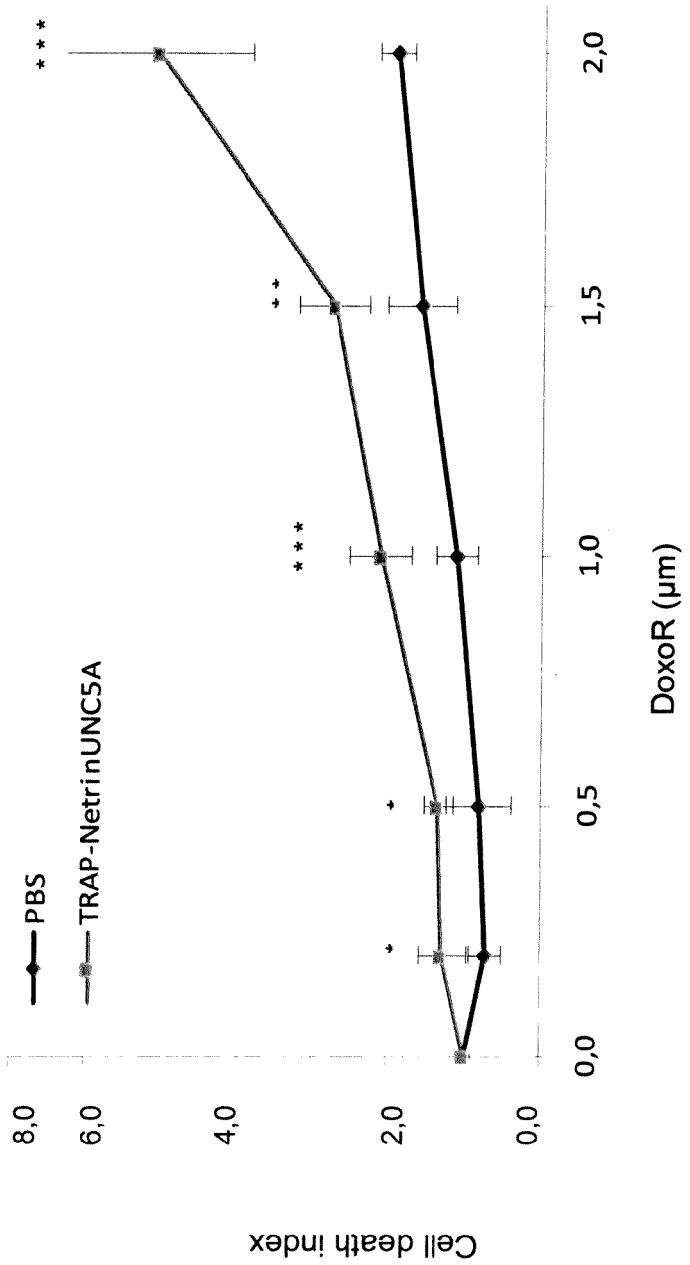

Cell death index
8,0
6,0
4,0
2,0
0,0
0,0
0,5
1,0
1,5
2,0
DoxoR (µm)
PBS
TRAP-NetrinUNC5A
*
*
***
**
***

Fig. 17

Fig.19

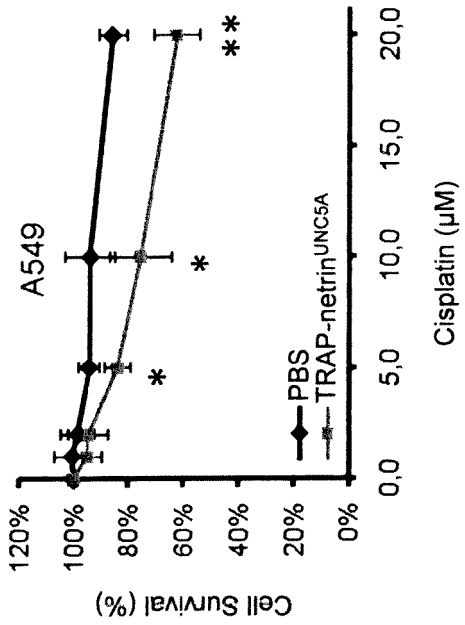

A549
PBS
TRAP-netrin^UNC5A
Cell Survival (%)
120%
100%
80%
60%
40%
20%
0%
0,0
5,0
10,0
15,0
20,0
Cisplatin (µM)

Fig.18

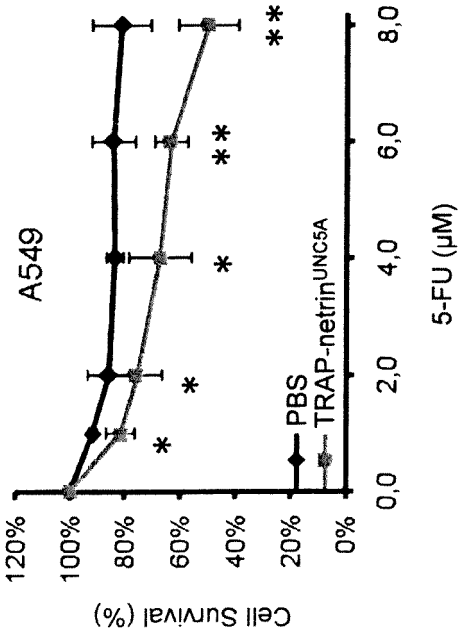

A549
PBS
TRAP-netrin^UNC5A
Cell Survival (%)
120%
100%
80%
60%
40%
20%
0%
0,0
2,0
4,0
6,0
8,0
5-FU (µM)

Fig.21

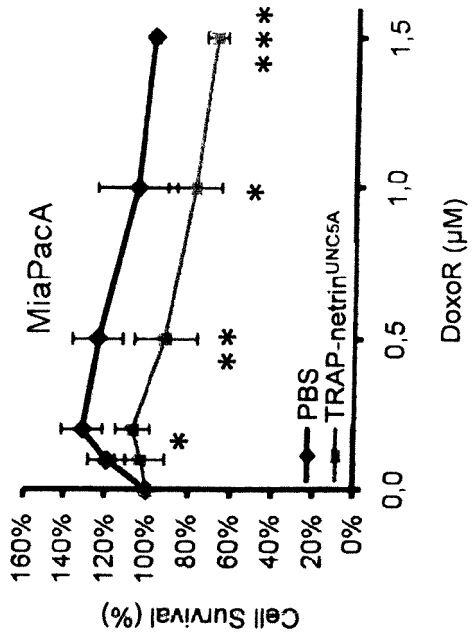

MiaPacA
Cell Survival (%)
160%
140%
120%
100%
80%
60%
40%
20%
0%
0,0
0,5
1,0
1,5
DoxoR (µM)
PBS
TRAP-netrin^UNC5A
*
**
***

Fig.20

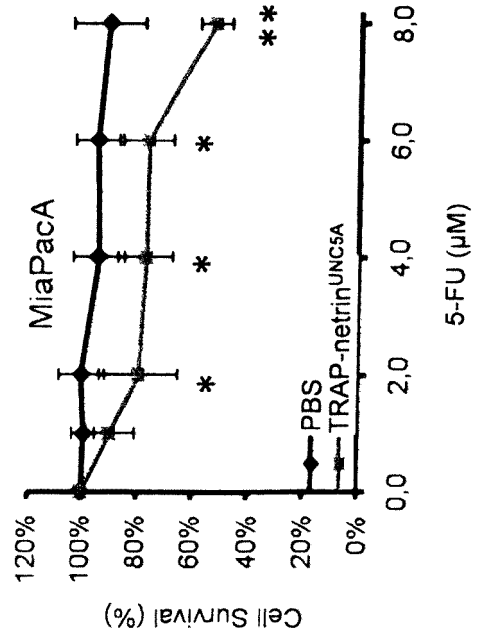

MiaPacA
Cell Survival (%)
120%
100%
80%
60%
40%
20%
0%
0,0
2,0
4,0
6,0
8,0
5-FU (µM)
PBS
TRAP-netrin^UNC5A
*
**

Fig. 22

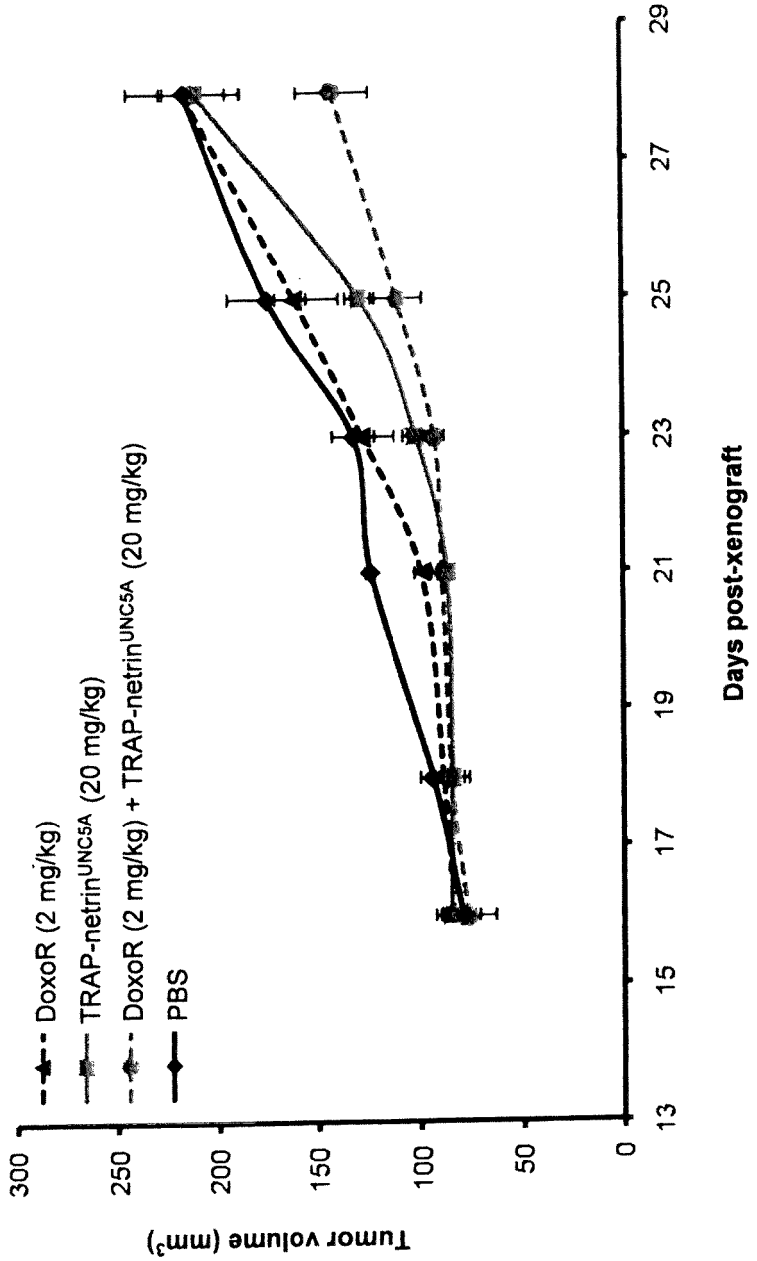
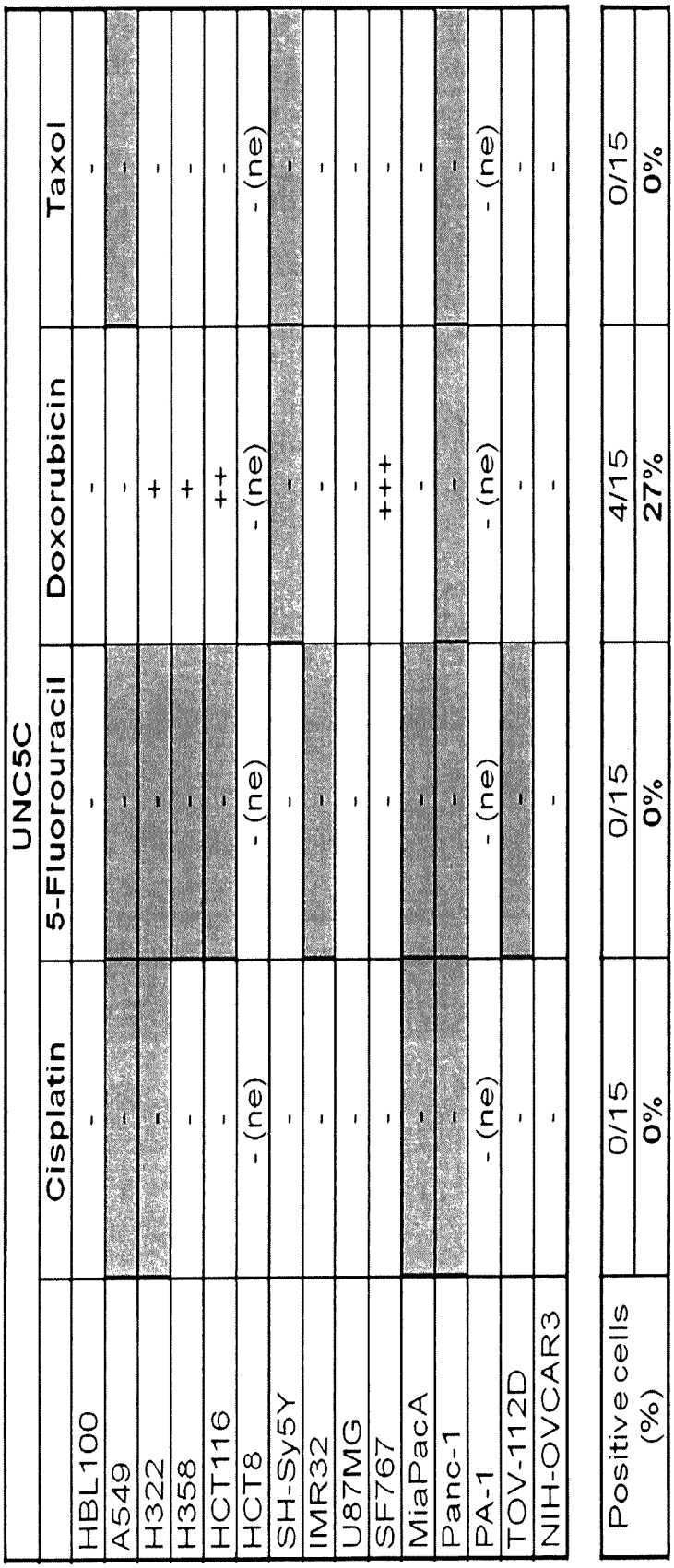

DoxoR (2 mg/kg)
TRAP-netrin^{UNC5A} (20 mg/kg)
DoxoR (2 mg/kg) + TRAP-netrin^{UNC5A} (20 mg/kg)
PBS
Tumor volume (mm^3)
300
250
200
150
100
50
0
13
15
17
19
21
23
25
27
29
Days post-xenograft

Fig. 23

UNC5A	Cisplatin	5-Fluorouracil	Doxorubicin	Taxol
HBL100	-	-	-	-
A549	-	-	++	-
H322	- (ne)	- (ne)	- (ne)	- (ne)
H358	- (ne)	- (ne)	- (ne)	- (ne)
HCT116	-	-	-	-
HCT8	- (ne)	- (ne)	- (ne)	- (ne)
SH-Sy5Y	-	-	-	-
IMR32	-	-	-	-
U87MG	- (ne)	- (ne)	- (ne)	- (ne)
SF767	- (ne)	- (ne)	- (ne)	- (ne)
MiaPacA	++	++	++	++
Panc-1	- (ne)	- (ne)	- (ne)	- (ne)
PA-1	- (ne)	- (ne)	- (ne)	- (ne)
TOV-112D	-	-	++	-
NIH-OVCAR3	-	-	++	+

Positive cells (%)	1/15	1/15	4/15	2/15
	7%	7%	27%	13%

Fig. 24



UNC5C	Cisplatin	5-Fluorouracil	Doxorubicin	Taxol
HBL100	-	-	-	-
A549	-	-	-	-
H322	-	-	+	-
H358	-	-	+	-
HCT116	-	-	++	-
HCT8	- (ne)	- (ne)	- (ne)	- (ne)
SH-Sy5Y	-	-	-	-
IMR32	-	-	-	-
U87MG	-	-	-	-
SF767	-	-	+++	-
MiaPacA	-	-	-	-
Panc-1	-	-	-	-
PA-1	- (ne)	- (ne)	- (ne)	- (ne)
TOV-112D	-	-	-	-
NIH-OVCAR3	-	-	-	-
Positive cells	0/15	0/15	4/15	0/15
(%)	0%	0%	27%	0%

Fig. 25

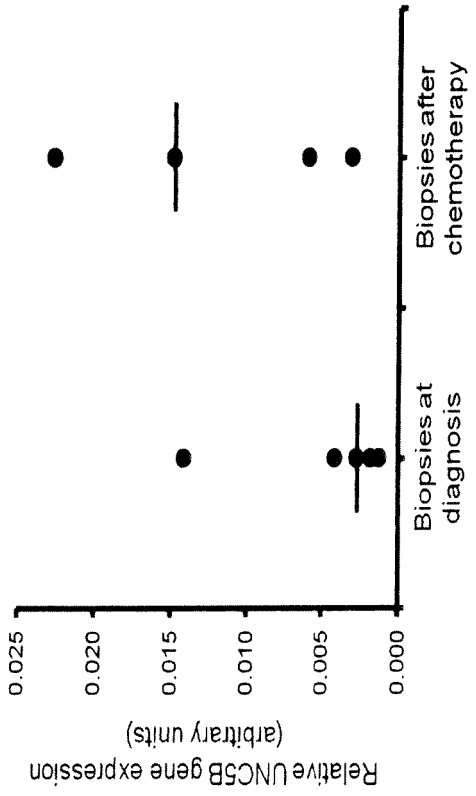


Fig. 26

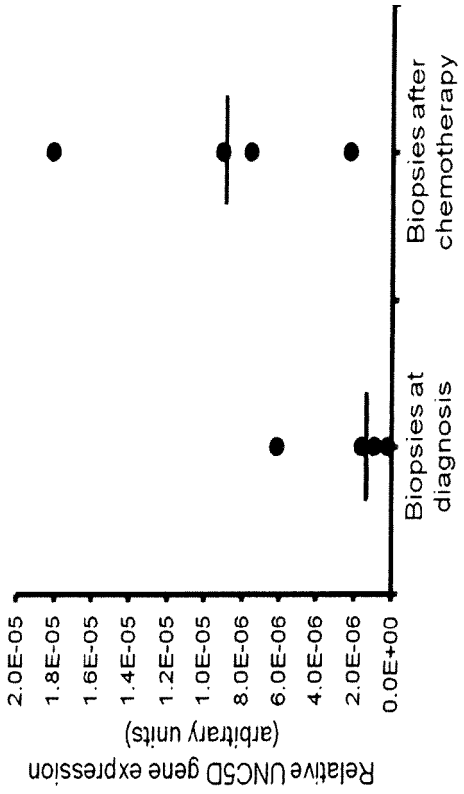
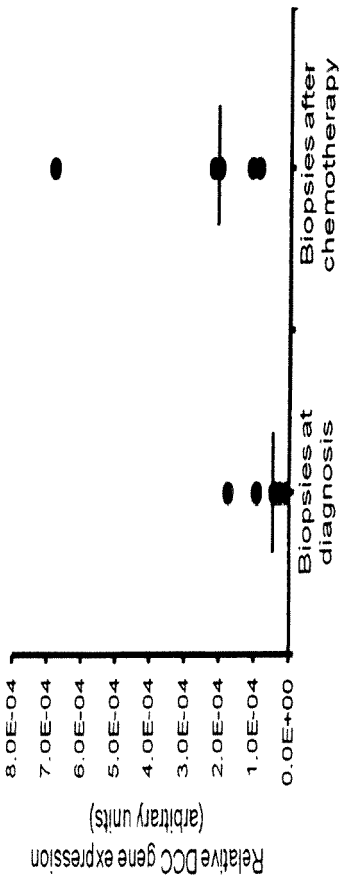


Fig. 27



SUBSTITUTE SHEET (RULE 26)

Fig. 28

	Cisplatin			5-Fluorouracil			Doxorubicin			Taxol		
	IC_{10}	IC_{30}	IC_{50}	IC_{10}	IC_{30}	IC_{50}	IC_{10}	IC_{30}	IC_{50}	IC_{10}	IC_{30}	IC_{50}
HBL100	0.5μM	1.5μM	2.5μM	0.036μM	0.108μM	0.18μM	0.04μM	0.12μM	0.2μM	0.6nM	1.8nM	3nM
A549	10μM[1]	25μM[2]	50μM[3]	0.4μM[1]	1μM[2]	2μM[3]	0.5μM	1.5μM	2.5μM	100nM[1]	250nM[2]	500nM[3]
H322	10μM[1]	25μM[2]	50μM[3]	0.4μM[1]	1μM[2]	2μM[3]	0.36μM	1.08μM	1.8μM	1nM	3nM	5nM
H358	0.48μM	1.44μM	2.4μM	0.4μM[1]	1μM[2]	2μM[3]	0.15μM	0.45μM	0.75μM	1nM	3nM	5nM
HCT116	7μM	21μM	35μM	4μM[1]	10μM[2]	20μM[3]	0.2μM	0.6μM	1μM	0.08nM	0.24nM	0.4nM
HCT8	1.2μM	3.6μM	6μM	0.25μM	0.75μM	1.25μM	0.36μM	1.08μM	1.8μM	4nM	12nM	20nM
SH-Sy5Y	0.35μM	1.05μM	1.75μM	0.03μM	0.09μM	0.15μM	1μM[1]	2.5μM[2]	5μM[3]	100nM[1]	250nM[2]	500nM[3]
IMR32	0.4μM	1.2μM	2μM	0.4μM[1]	1μM[2]	2μM[3]	0.2μM	0.6μM	1μM	0.3nM	0.9nM	1.5nM
U87MG	1.24μM	3.72μM	6.2μM	0.25μM	0.75μM	1.25μM	0.2μM	0.6μM	1μM	2nM	6nM	10nM
SF767	0.4μM	1.2μM	2μM	0.46μM	1.38μM	2.3μM	0.24μM	0.72μM	1.2μM	1nM	3nM	5nM
MiaPacA	10μM[1]	25μM[2]	50μM[3]	0.4μM[1]	1μM[2]	2μM[3]	0.76μM	2.28μM	3.8μM	1nM	3nM	5nM
Panc-1	10μM[1]	25μM[2]	50μM[3]	0.4μM[1]	1μM[2]	2μM[3]	1μM[1]	2.5μM[2]	5μM[3]	100nM[1]	250nM[2]	500nM[3]
PA-1	0.12μM	0.36μM	0.6μM	0.6μM	1.8μM	3μM	0.16μM	0.48μM	0.8μM	0.8nM	2.4nM	4nM
TOV-112D	1.46μM	4.4μM	7.3μM	4.88μM	14.64μM	24.4μM	0.34μM	1.02μM	1.7μM	10.4nM	31.1nM	51.9nM
NIH-OVCAR3	2.8μM	8.5μM	14.1μM	1.72μM	5.16μM	8.6μM	0.68μM	2.04μM	3.4μM	6.3nM	18.9nM	31.5nM

[1], 1/5 IC_{MAX} ; [2], 1/2 IC_{MAX}; [3], IC_{MAX}

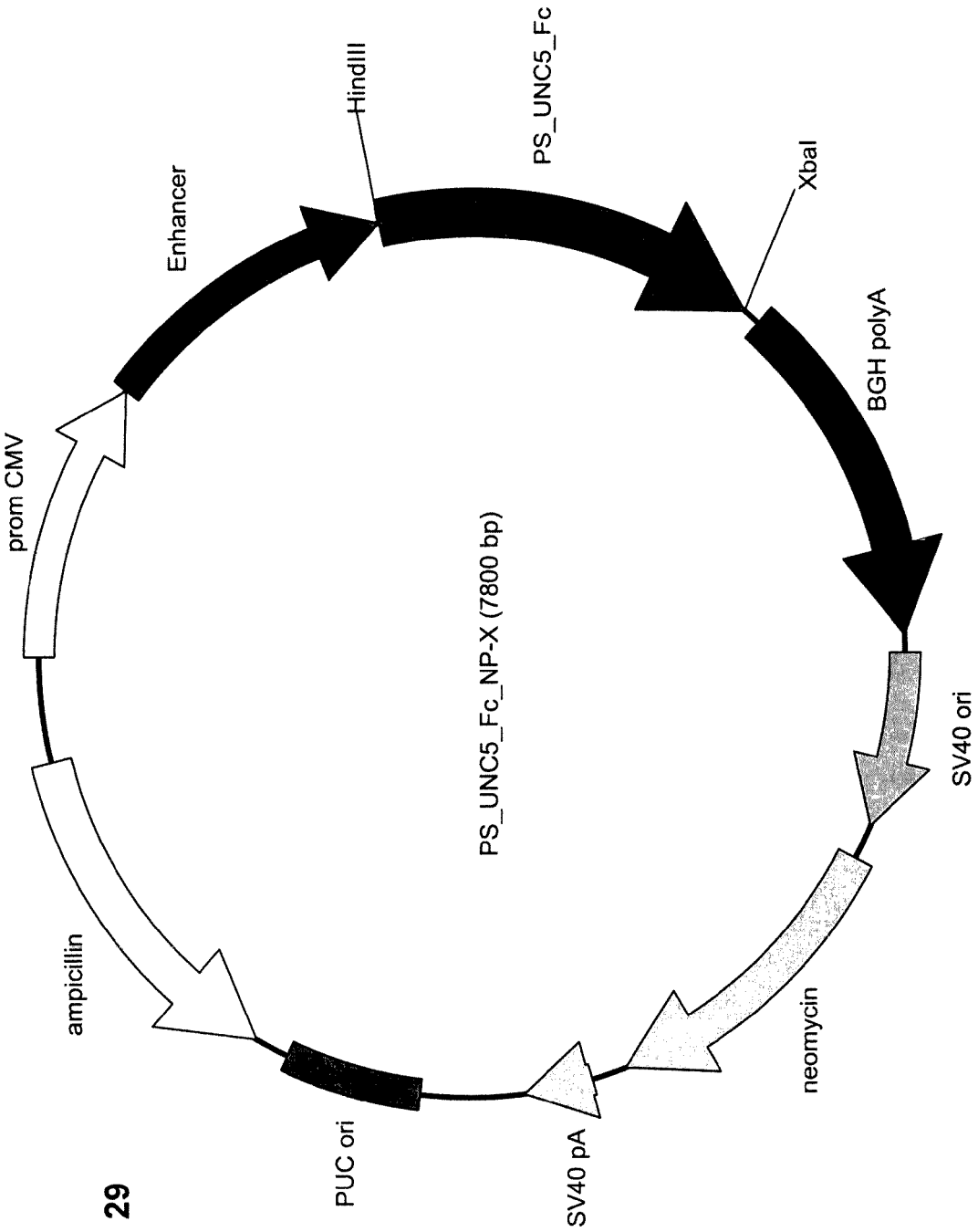

PS_UNC5_Fc_NP-X (7800 bp)
prom CMV
Enhancer
HindIII
PS_UNC5_Fc
XbaI
BGH polyA
SV40 ori
neomycin
SV40 pA
PUC ori
ampicillin

Fig. 29