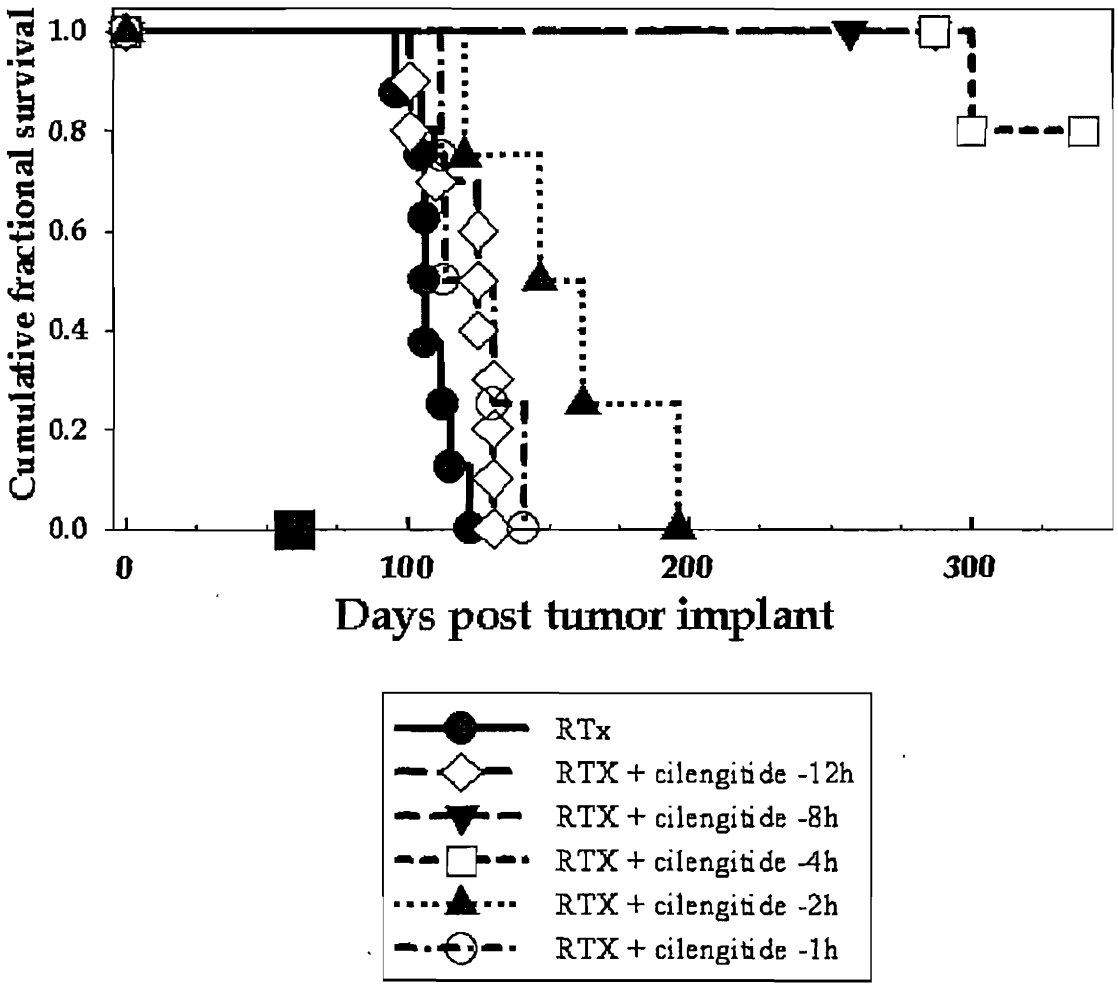
Figure 1

Kaplan Meier survival curves of nude rats bearing orthotopic human glioblastomas U251 derived.



Dark square represents survival of non irradiated animals.

Figure 2

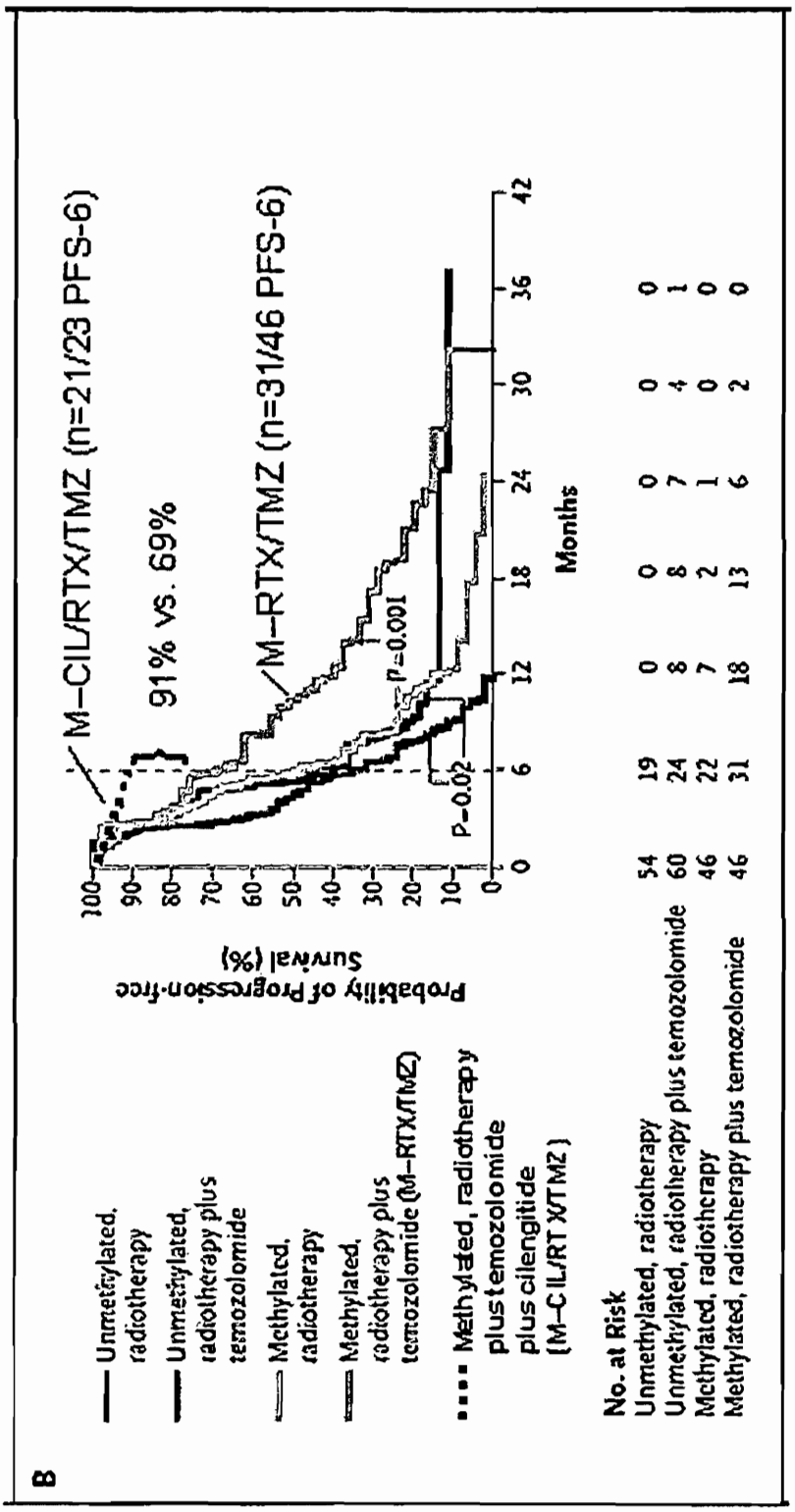
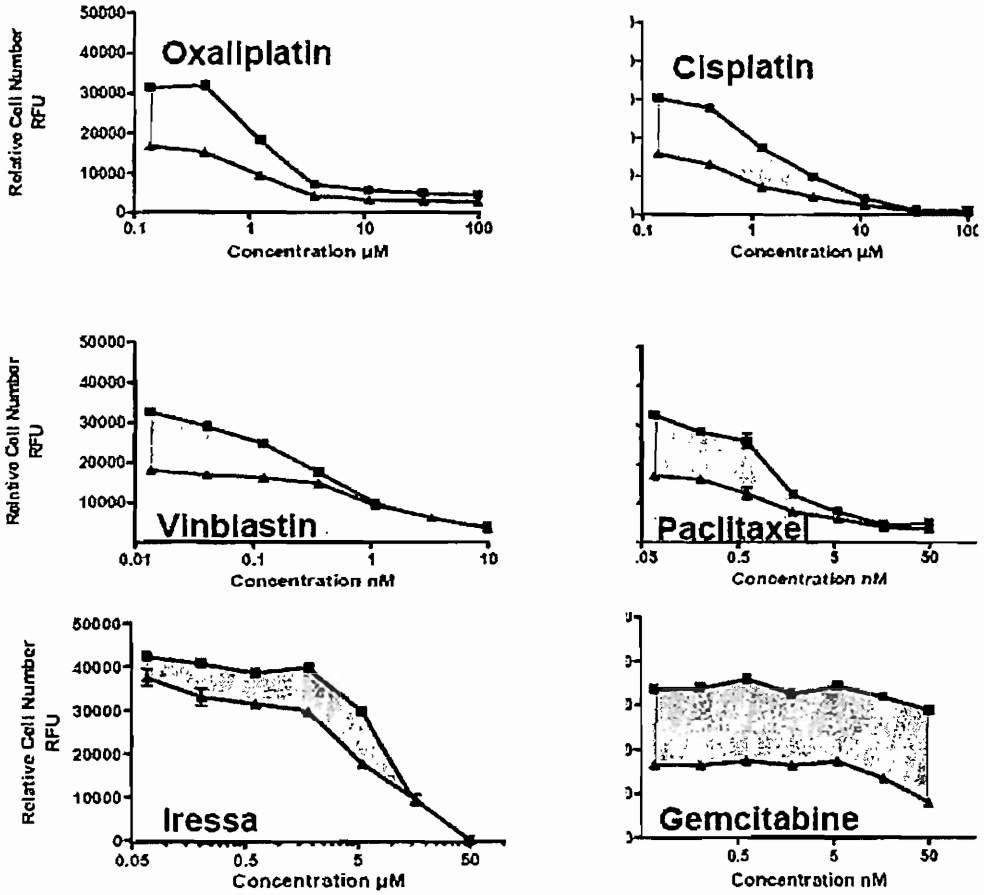

B
Unmethylated, radiotherapy
Unmethylated, radiotherapy plus temozolomide
Methylated, radiotherapy
Methylated, radiotherapy plus temozolomide (M-RTX/TMZ)
Methylated, radiotherapy plus temozolomide plus cilengitide (M-CIL/RTX/TMZ)
Probability of Progression-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
6
12
18
24
30
36
42
Months
M-CIL/RTX/TMZ (n=21/23 PFS-6)
91% vs. 69%
M-RTX/TMZ (n=31/46 PFS-6)
P=0.001
P=0.02
No. at Risk
Unmethylated, radiotherapy 54 19 0 0 0 0 0
Unmethylated, radiotherapy plus temozolomide 60 24 8 8 7 4 1
Methylated, radiotherapy 46 22 7 2 1 0 0
Methylated, radiotherapy plus temozolomide 46 31 18 13 6 2 0

Figure 3

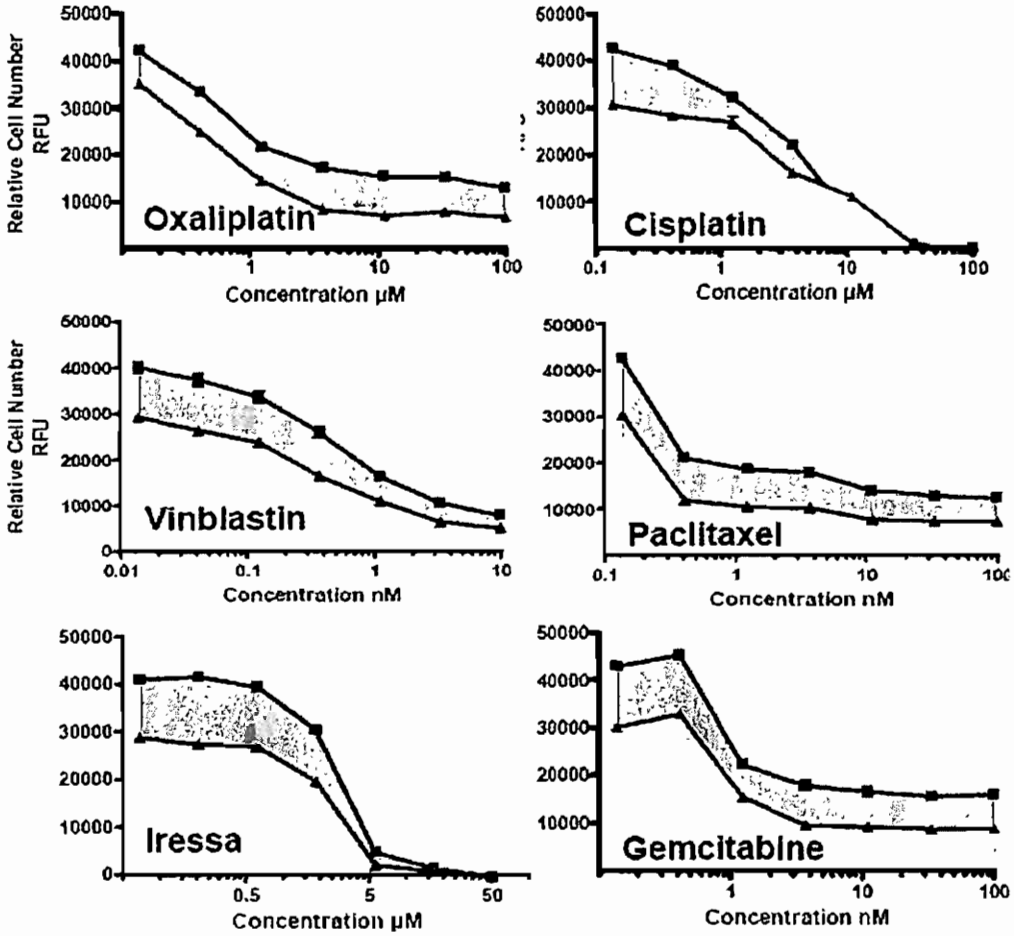
NSCLC (A549)



Squares – Chemotherapeutic alone
Triangles – Chemotherapeutic plus Cilengitide 6 uM constant

Figure 4

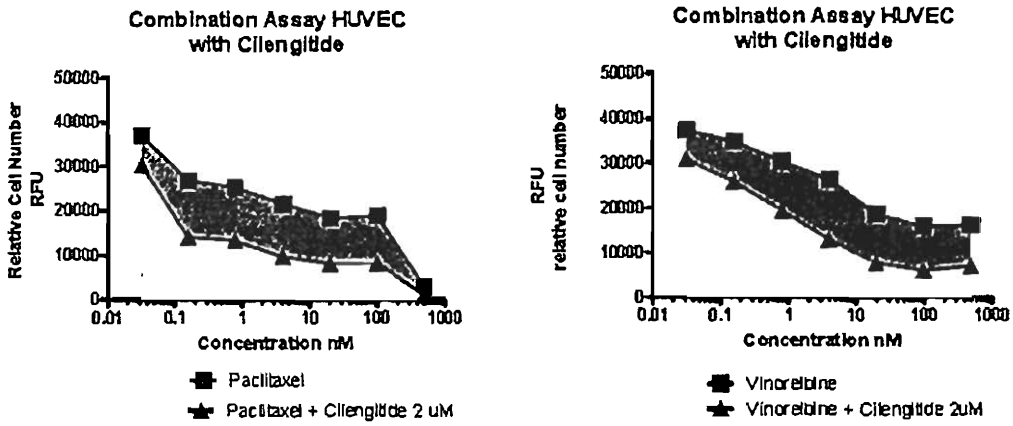
Endothelial Cells (HUVEC)



Squares – Chemotherapeutic alone
Triangles – Chemotherapeutic plus Cilengitide 0.2 uM constant

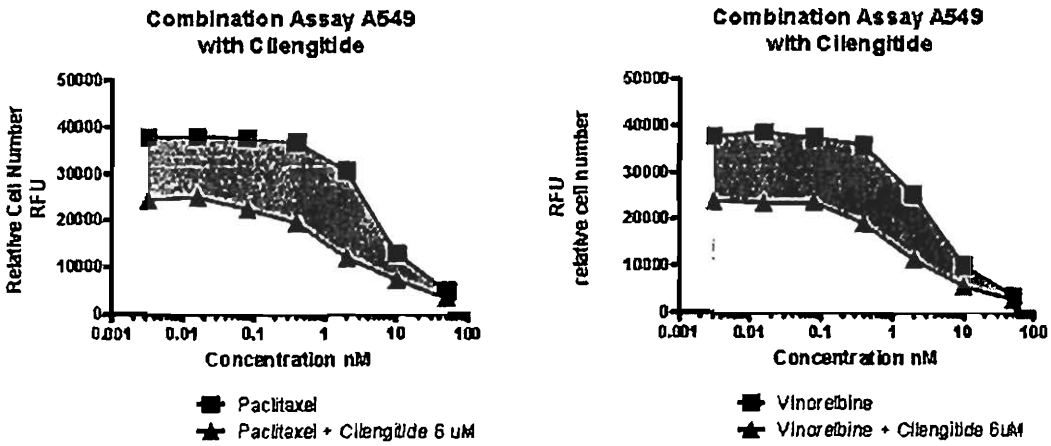
Figure 5

Effect of αv integrin ligand Cilengitide in combination with paclitaxel or vinorelbine on HUVEC cell proliferation:



	Paclitaxel	Paclitaxel + Cilengitide 2 uM	Vinorelbine	Vinorelbine + Cilengitide 2uM
Bottom	~3000	6084	14610	5675
Top	45874	~47000	37836	33533
LogIC50	0.09583	-1.377	0.4511	-0.1391
HillSlope	-0.2770	-0.6878	-0.6954	-0.6821
IC50	1.247	0.04199	2.826	0.7260

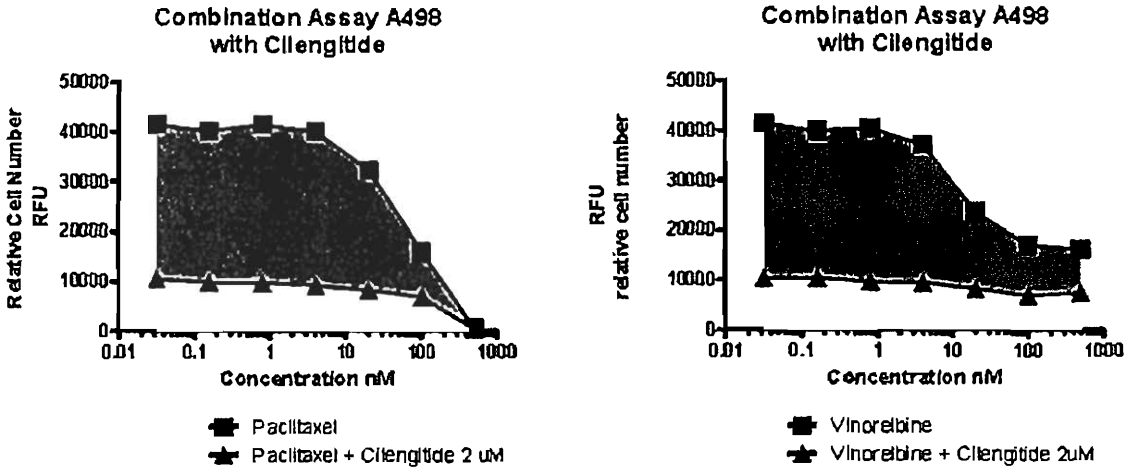
Effect αv integrin ligand Cilengitide in combination with paclitaxel or vinorelbine on NSCLC cells



	Paclitaxel	Paclitaxel + Cilengitide 6 uM	Vinorelbine	Vinorelbine + Cilengitide 6uM
Bottom	3635	1871	2043	2126
Top	37578	24772	37852	23887
LogIC50	0.6943	0.2154	0.5267	0.1671
HillSlope	-1.415	-0.7402	-1.177	-0.9520
IC50	4.946	1.642	3.362	1.469

Figure 6

Effect αv integrin ligand Cilengitide in combination with paclitaxel or vinorelbine on renal carcinoma cell proliferation.



	Paclitaxel	Paclitaxel + Cilengitide 2 uM	Vinorelbine	Vinorelbine + Cilengitide 2uM
Bottom	~ 2000	~ 2000	16181	6944
Top	40835	9607	40684	10252
LogIC50	1.761	~ 2.032	1.070	0.9869
HillSlope	-1.356	~ -8.656	-1.617	-1.023
IC50	57.73	~ 107.6	11.74	9.703

Effect αv integrin ligand Cilengitide in combination with vinorelbine or etoposide on SCCHN cell proliferation:

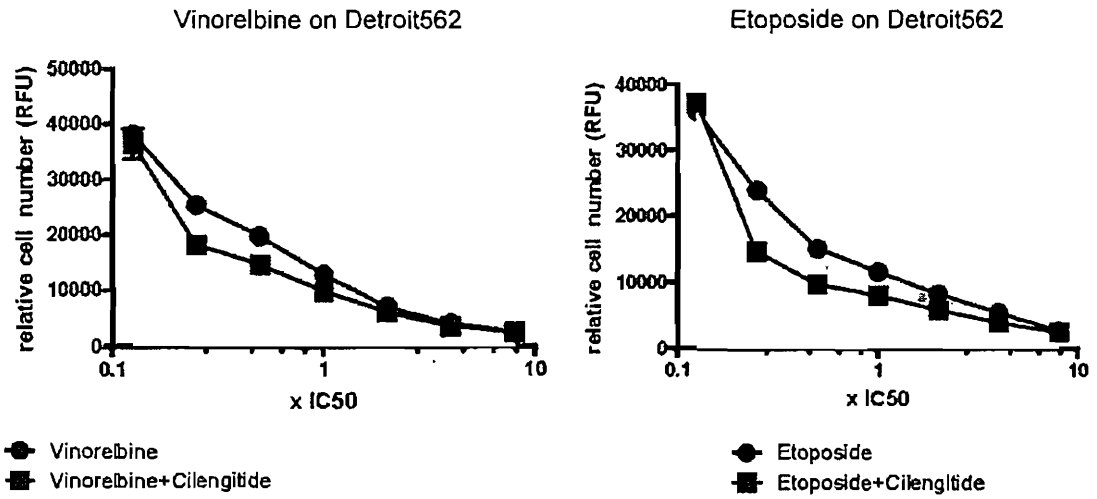
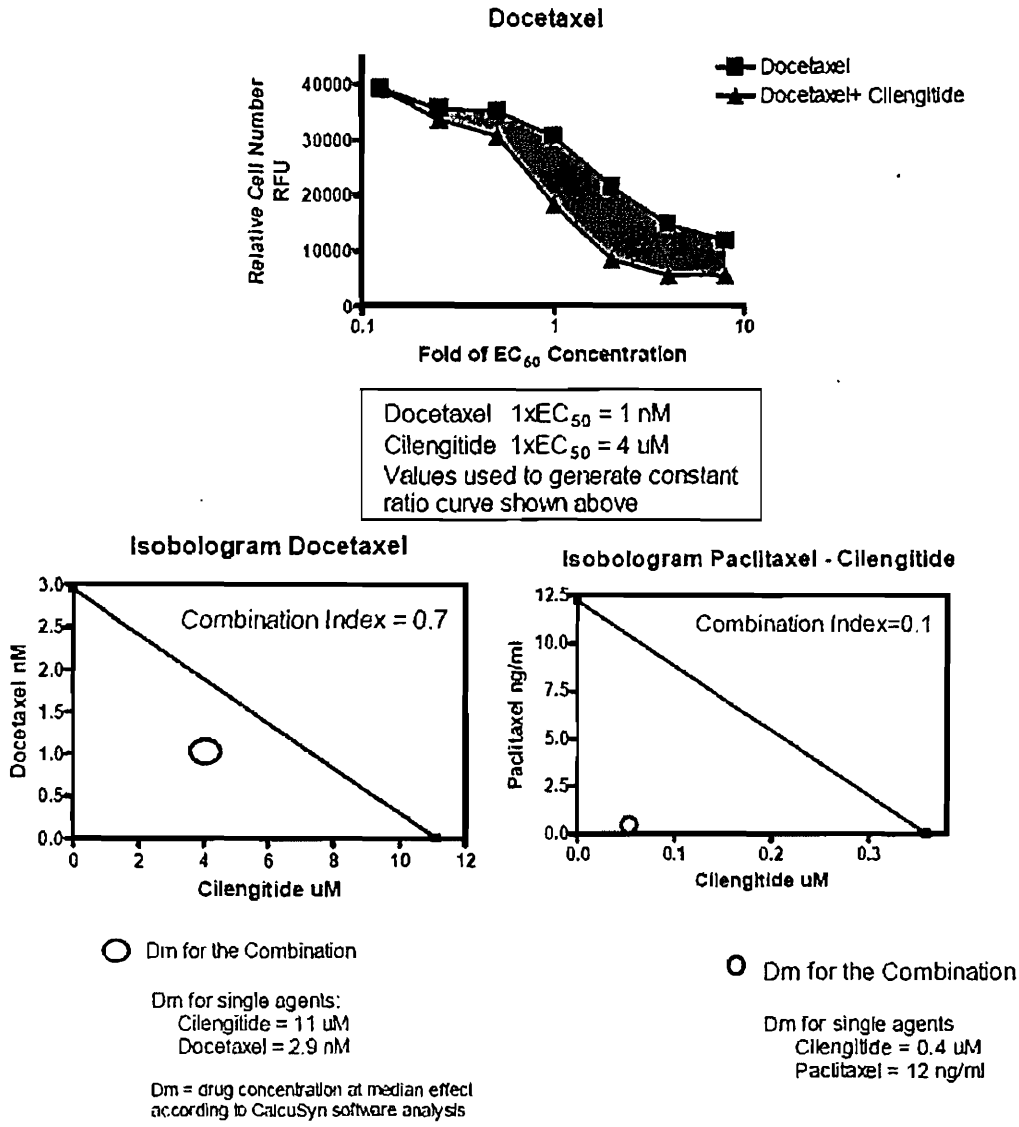


Figure 7

Effect of αv integrin ligand Cilengitide in combination with docetaxel on HUVEC cell proliferation:

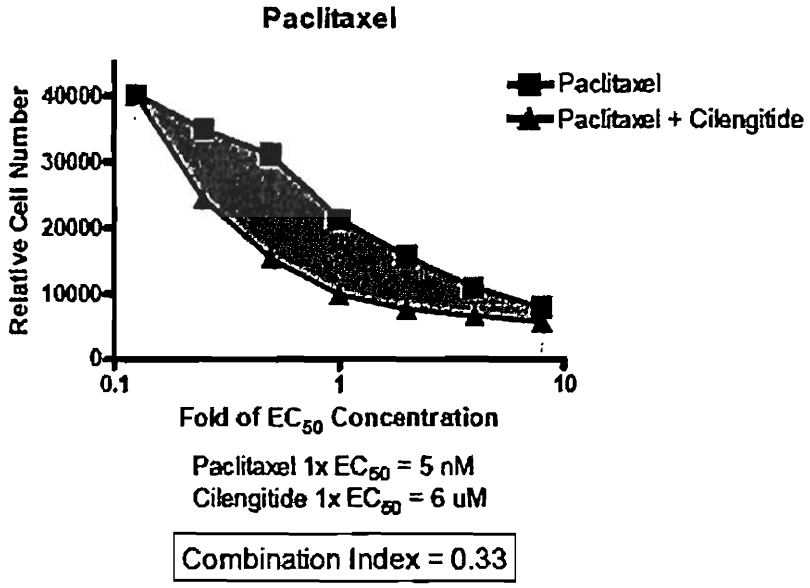
Constant ratio assay with docetaxel/paclitaxel and Cilengitide combinations on HUVEC endothelial cells grown in complete EGM MV medium, analysis according to Chou and Talalay [1] shows synergistic effect in Figure 7 graph and isobologram.



Combination Index (CI) < 1 shows synergistic effect of the respective combination

Figure 8

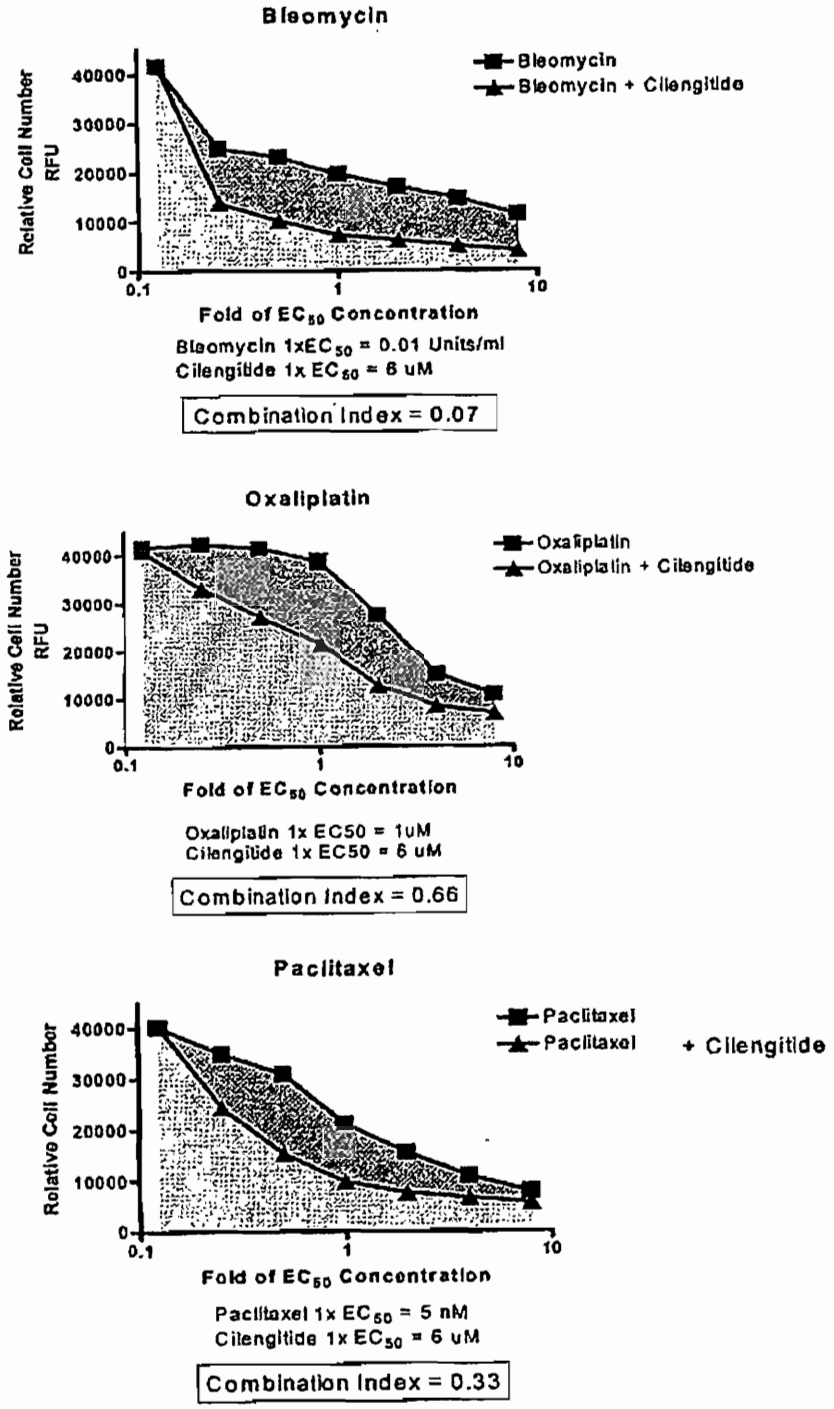
Effect of αv integrin ligand Cilengitide in combination with paclitaxel on A549 NSCLC cell proliferation:



Combination Index (CI) < 1 shows synergistic effect of the respective combination

Figure 9

Effect of αv integrin ligand Cilengitide in combination with bleomycin/oxaliplatin/paclitaxel on A549 NSCLC cell proliferation

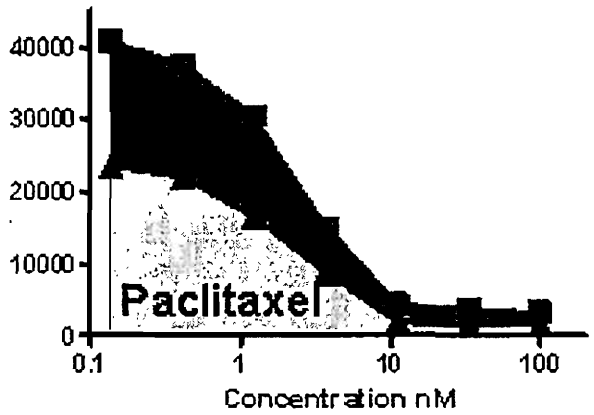


Combination Index (CI) < 1 shows synergistic effect of the respective combination

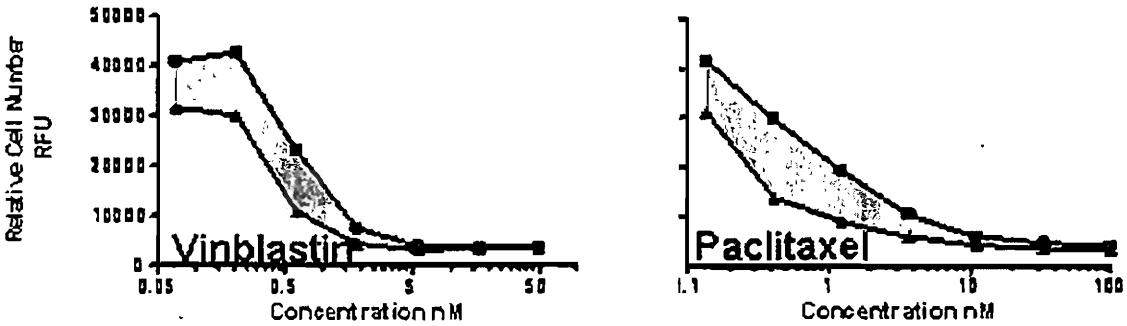
Figure 10

Effect of αv integrin ligand Cilengitide in combination with Paxlitaxel/Vinblastine on various NSCLC cell lines:

Cilengitide in combination with paclitaxel on NSCLC cell line Calu 6



Cilengitide in combination with Vinblastine/Paclitaxel on NSCLC cell line H460

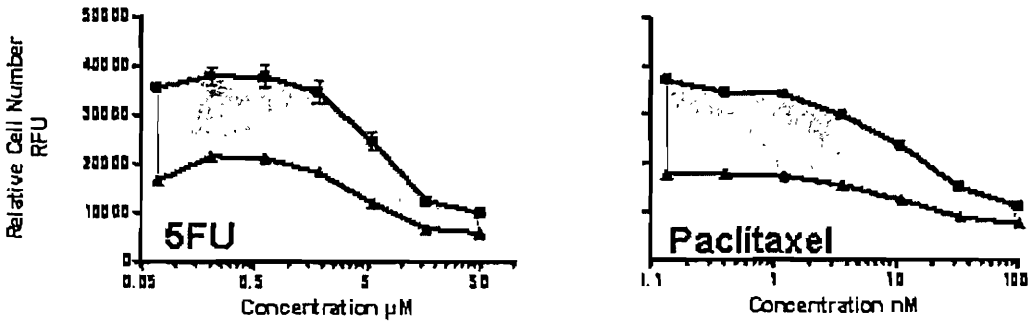


Serially dilute Vinblastine/Paclitaxel (squares) in presence of 10 uM cilengitide (triangles)

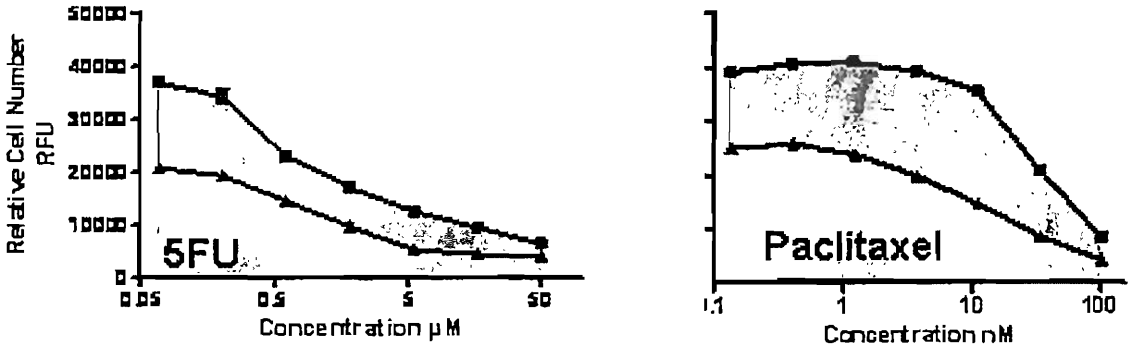
Figure 11

Effect of αv integrin ligand Cilengitide in combination with 5-FU/Paclitaxel on various EGFR dependent cell lines

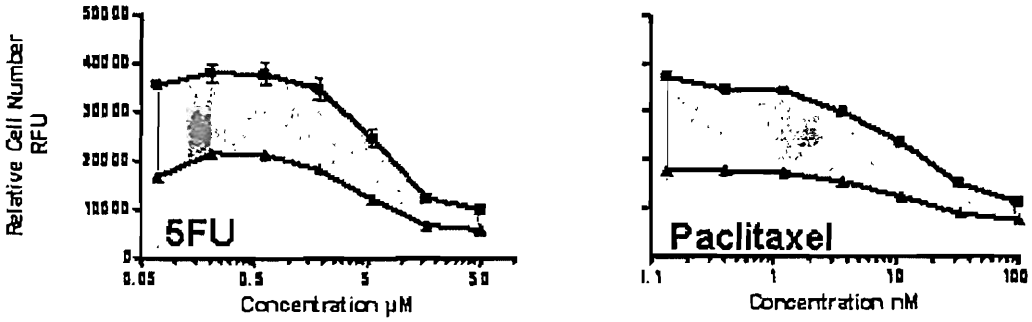
5-FU or Paxlitaxel on Renal cell line ACHN; Cilengitide constant at 2 µM



5-FU or Paxlitaxel on Renal cell line A498; Cilengitide constant at 2 µM



5-FU or Paxlitaxel on Renal cell line Caki 1; Cilengitide constant at 2 µM



Serially dilute 5-FU/Paclitaxel (squares) in presence of Cilengitide (triangles)

Figure 12

Combination efficacy of Cilengitide & Erbitux in carcinoma xenograft

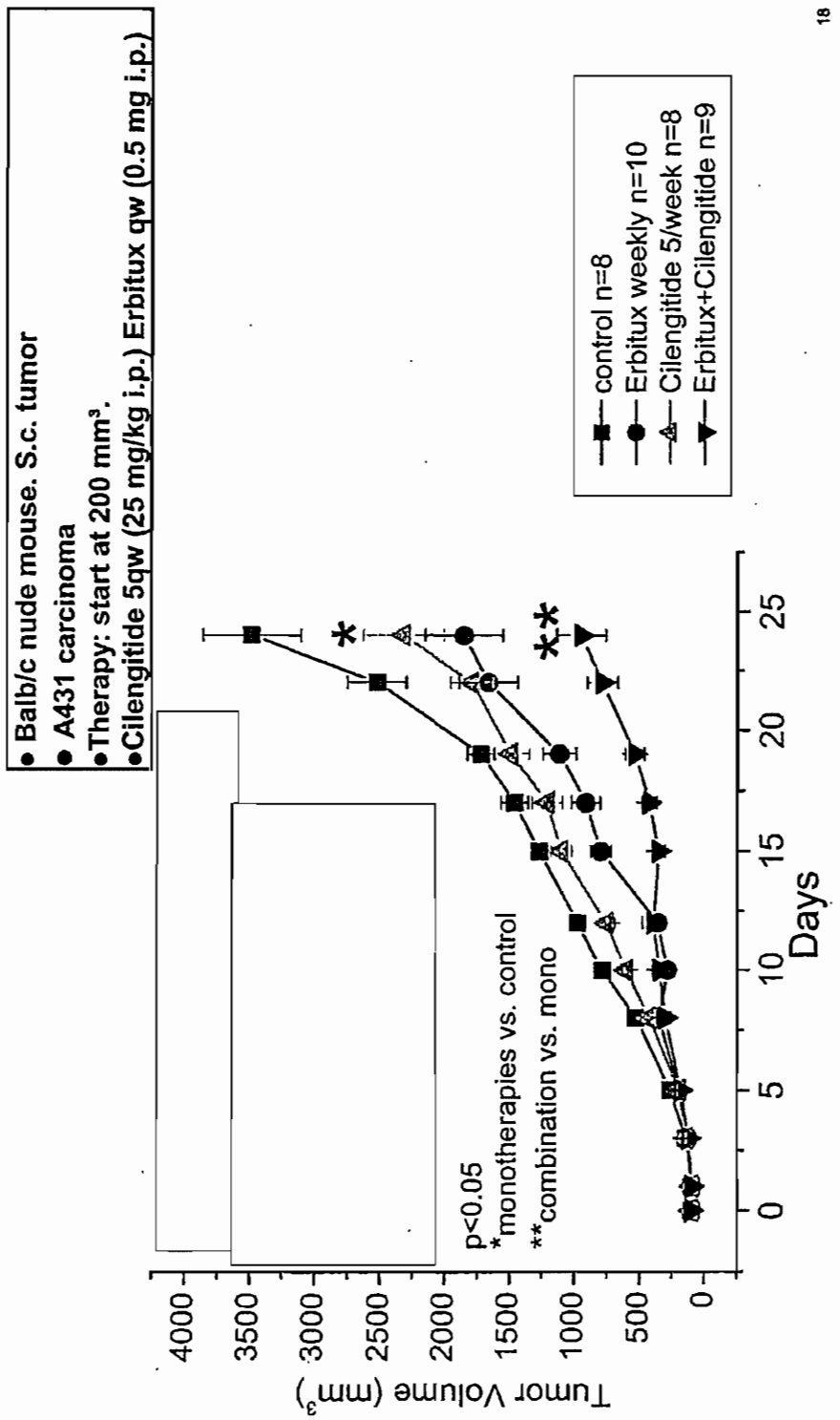
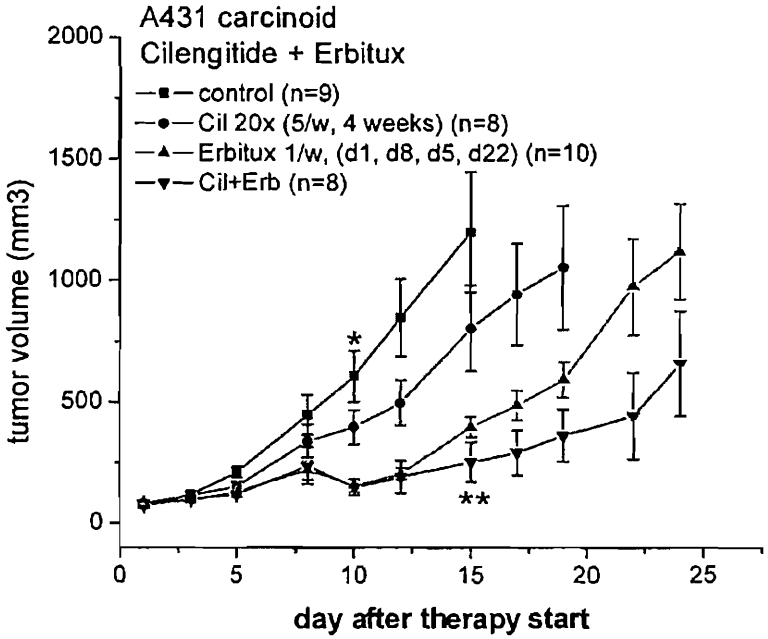


Figure 13

Combination efficacy of Cilengitide & Erbitux in carcinoma xenograft, optionally in combination with Radiotherapy (Rx); A431 human epidermoid carcinoma s.c. on balb c nu nu mouse; Erbitux: 25 mg/kg (=0.5mg/animal) i.p. d1 (4h pre Rx), d8, d15, d22,; Cilengitide: 25 mg/kg i.p. 20x 5/w 1-2 h pre Rx



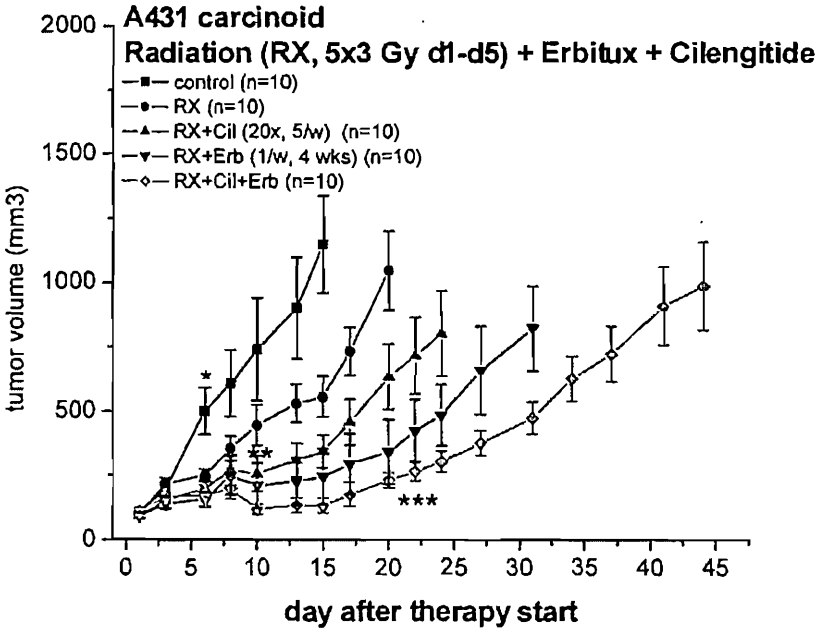


Figure 14

Combination efficacy of Cilengitide & Erbitux in A431/HDMVEC/U87 proliferation assay, optionally in combination with Radiotherapy (Rx)

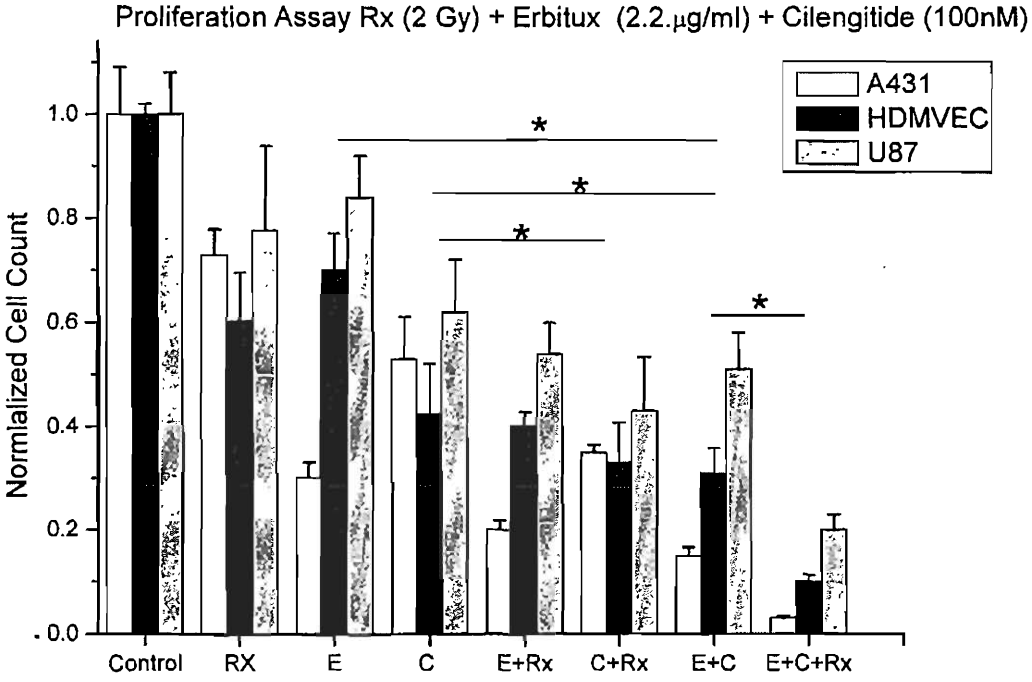
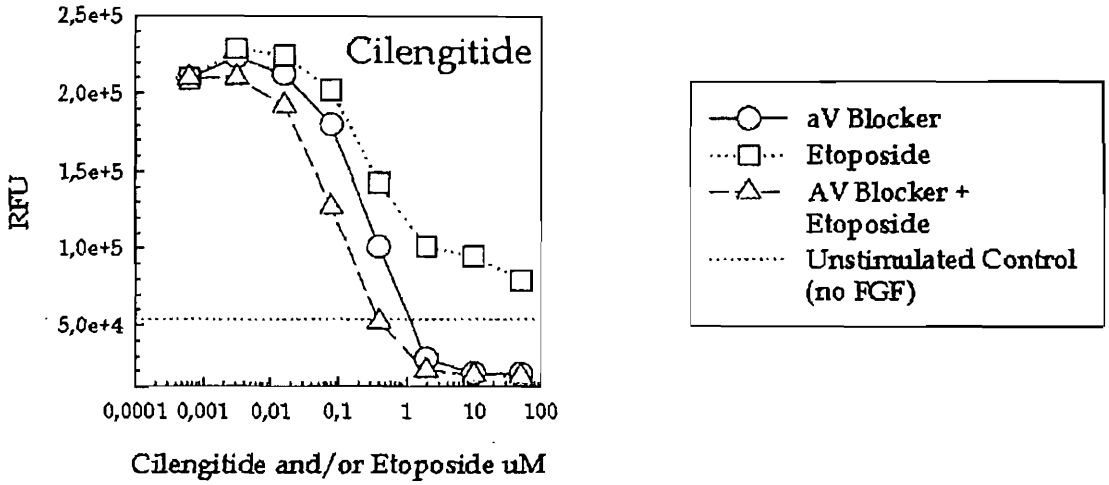
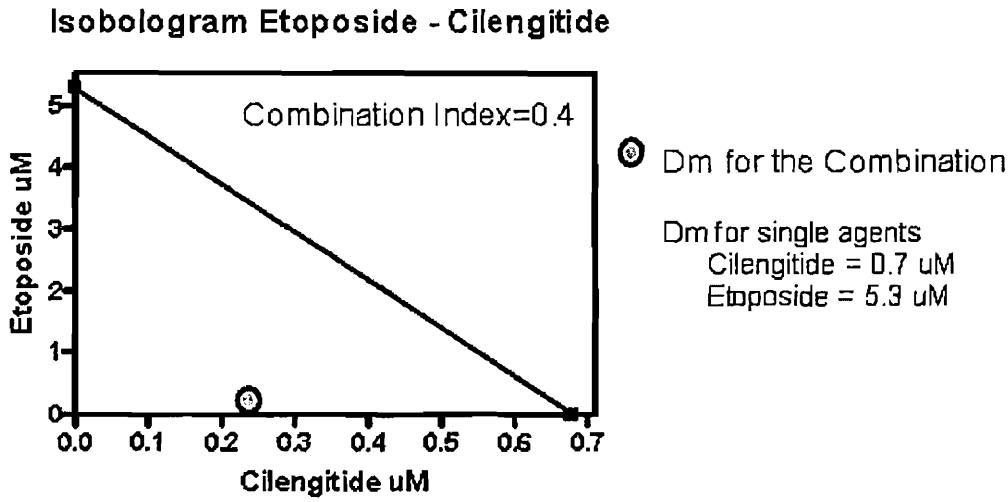


Figure 15

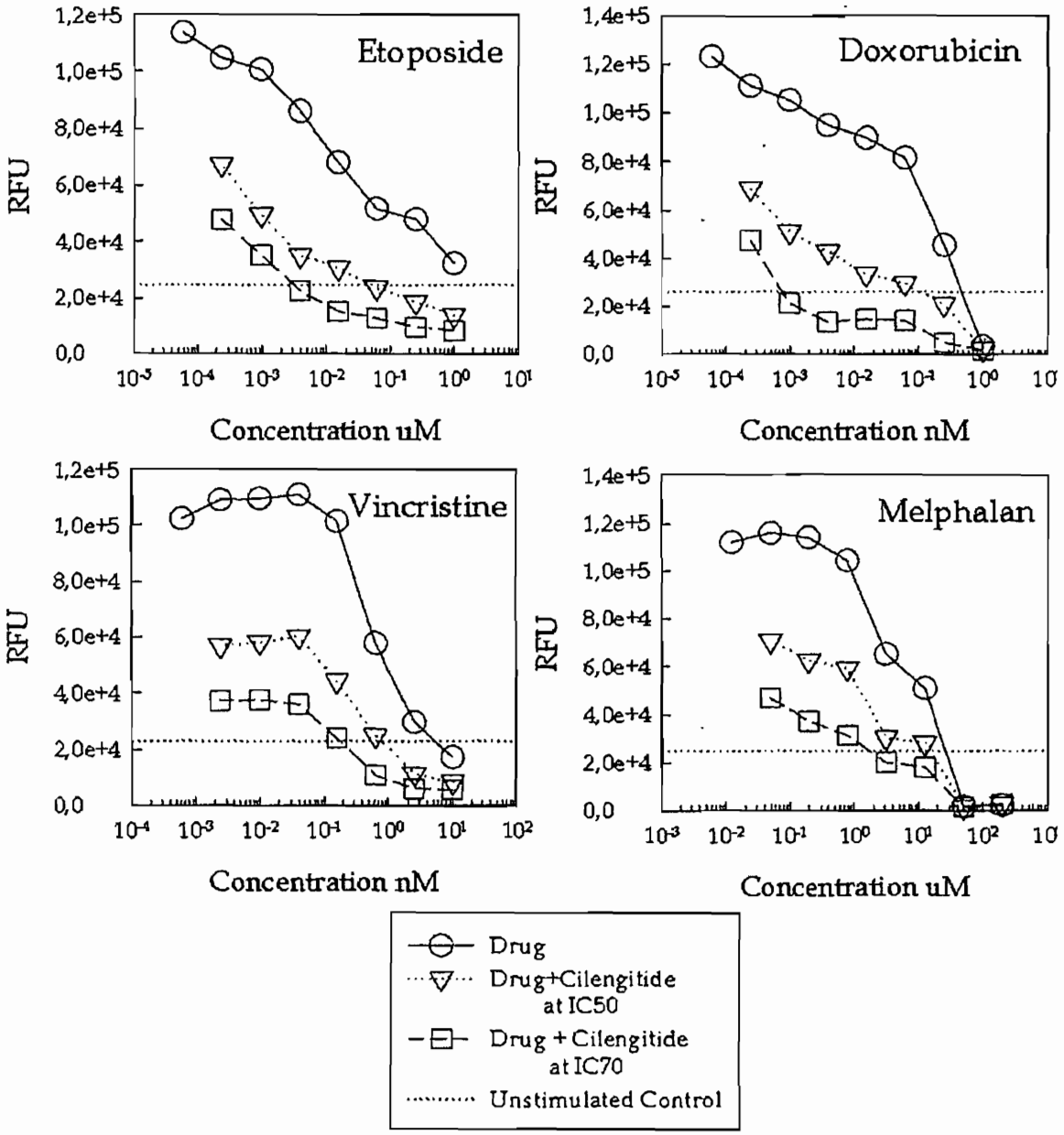


Effect of αv integrin ligand Cilengitide and etoposide on HUVEC cell proliferation. HUVEC cells were cultured on vitronectin-coated wells in Medium 199 containing 2% FSC and 10 ng/ml FGF-2 in the presence or absence of αv integrin ligand Cilengitide and the respective chemotherapeutic agent alone or in combination. Relative cell number was determined by Alamar Blue reduction.



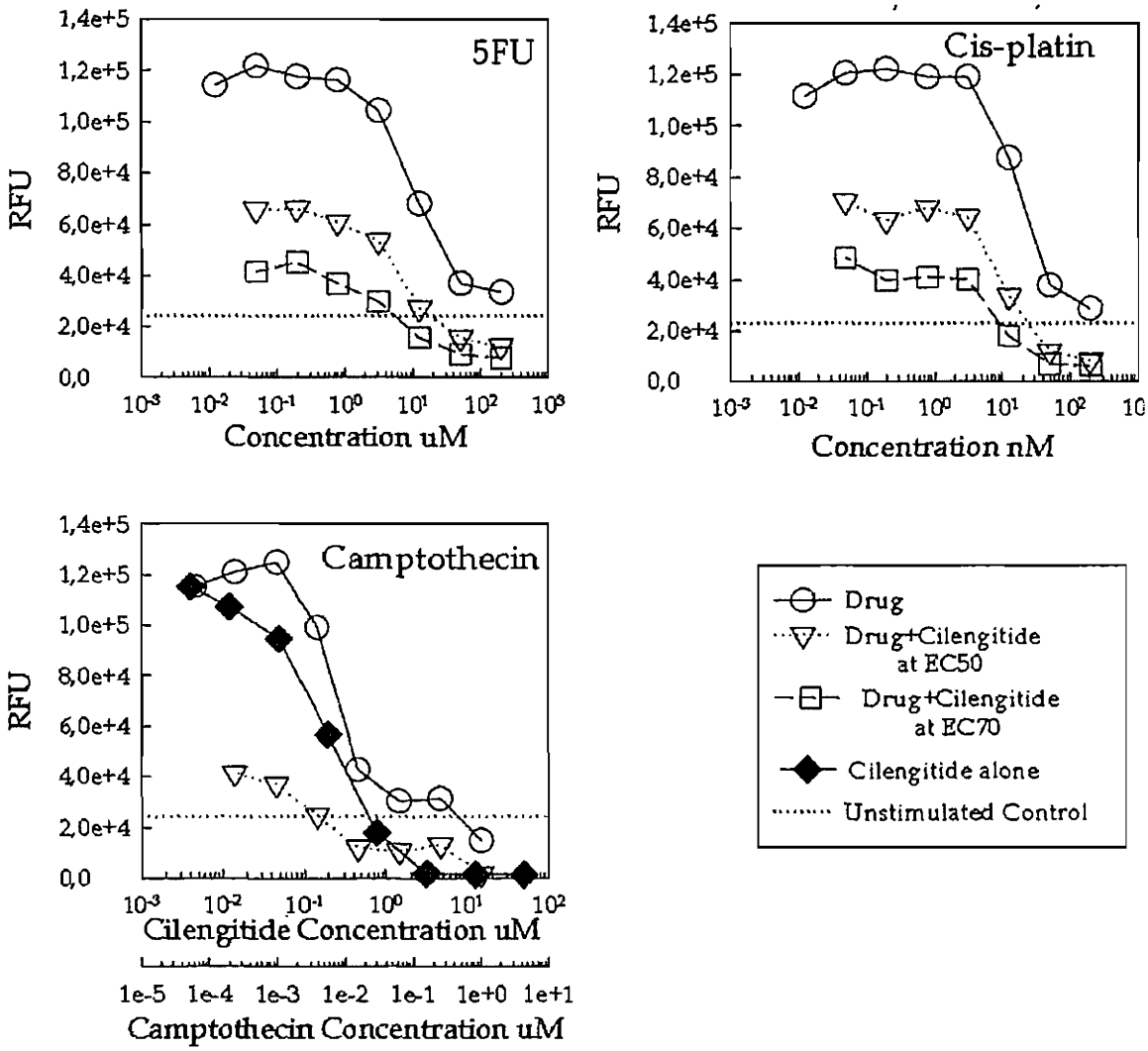
αv integrin ligand Cilengitide and etoposide act synergistically to inhibit HUVEC endothelial cell proliferation. Data presented in the graph above is additionally represented as isobologram and analysis according to Chou and Talalay [1]. Dm = drug concentration at medium effect. Combination Index (CI) < 1 indicates synergy.

Figure 16



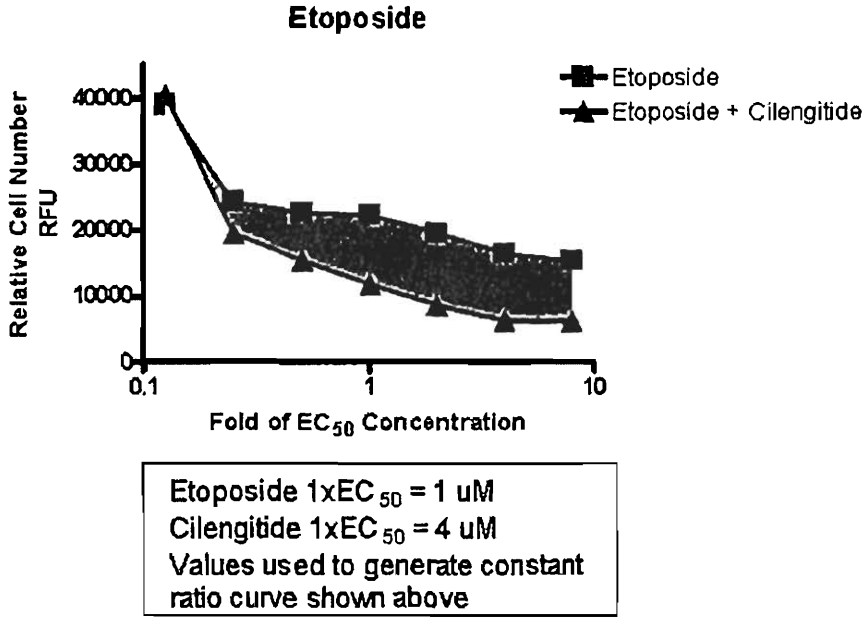
Effect of αv integrin ligand Cilengitide and the Drugs etoposide, doxorubicine, vincristine or melphalan on HUVEC cell proliferation.
HUVEC cells were cultured on vitronectin-coated wells in Medium 199 containing 2% FSC and 10 ng/ml FGF-2 in the presence or absence of αv integrin ligand Cilengitide and the respective chemotherapeutic agents (Drug) alone or in combination with a constant concentration(IC_{50} or IC_{70}) of Cilengitide. Related cell number was determined by Alamar Blue reduction.

Figure 17



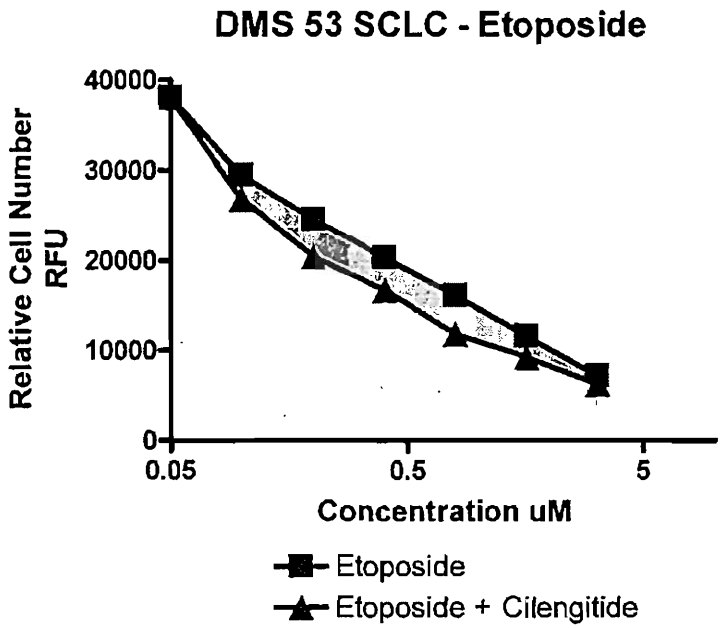
Effect of αv integrin ligand Cilengitide and the Drugs 5-FU, Cisplatin or Camptothecin on HUVEC cell proliferation.
HUVEC cells were cultured on vitronectin-coated wells in Medium 199 containing 2% FSC and 10 ng/ml FGF-2 in the presence or absence of αv integrin ligand Cilengitide and the respective chemotherapeutic agents (Drug) alone or in combination with a constant concentration(IC_{50} or IC_{70}) of Cilengitide. Related cell number was determined by Alamar Blue reduction.

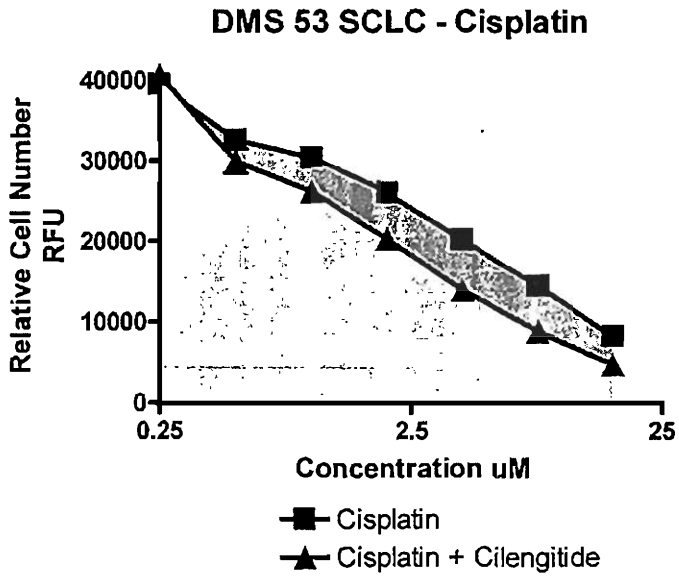
Figure 18



Constant ratio assay with etoposide and cilengitide combinations on HUVEC cells grown in comlpete EGM MV medium, analysis according to Chou and Talalay [1].

Figure 19





Constant Ratio Proliferation Assay:
Cells were cultured 72 hr in the presence of etoposide or cisplatin alone or in combination with Cilengitide at a fixed ratio. Cell number was determined by Alamar Blue reduction. X-axis shows the concentration of chemotherapeutic agent used. The Cilengitide concentration was in a ratio of 0.4:1 for etoposide:Cilengitide and 1:0.5 for cisplatin:Cilengitide.