FIGURE 1

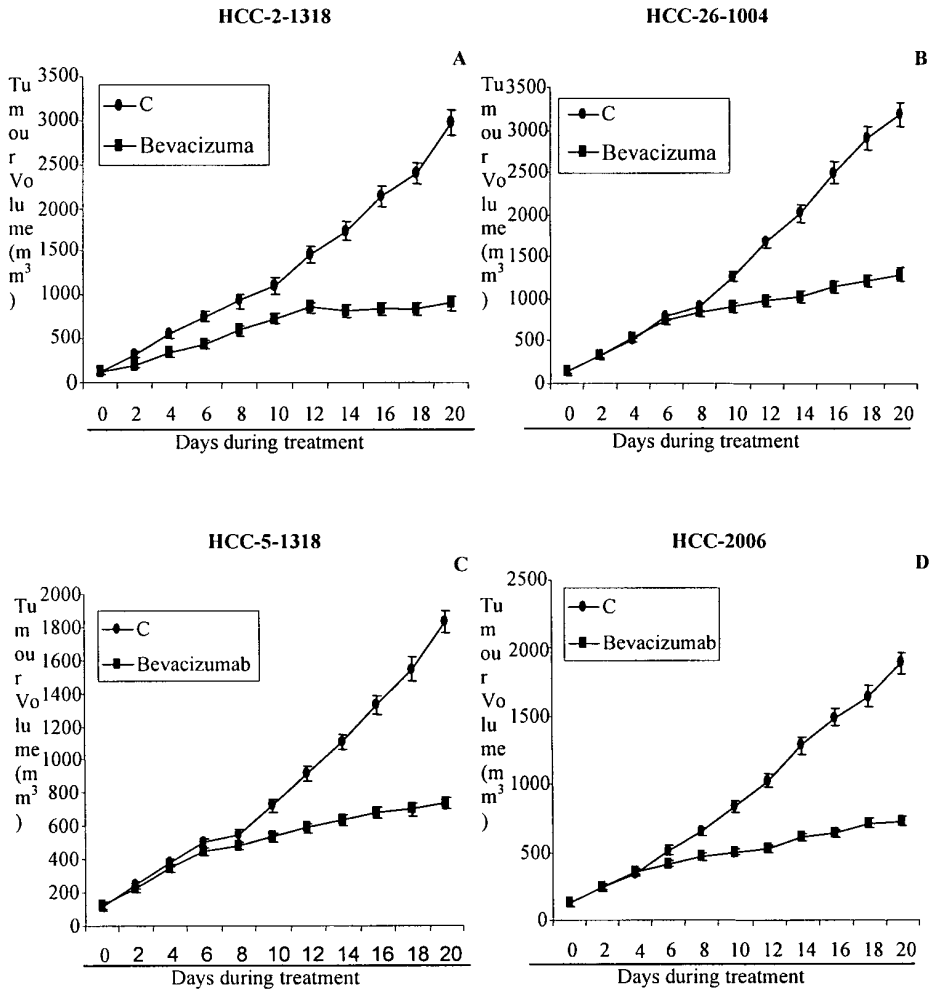


Figure 1

FIGURE 2

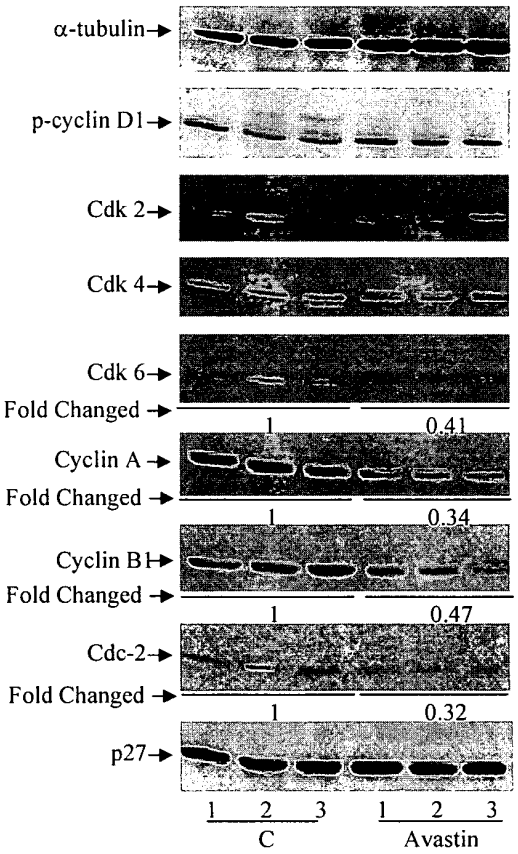

α-tubulin
p-cyclin D1
Cdk 2
Cdk 4
Cdk 6
Fold Changed
1
0.41
Cyclin A
Fold Changed
1
0.34
Cyclin B1
Fold Changed
1
0.47
Cdc-2
Fold Changed
1
0.32
p27
1 2 3
1 2 3
C
Avastin

FIGURE 3A



C Bevacizumab

FIGURE 3B



FIGURE 3C

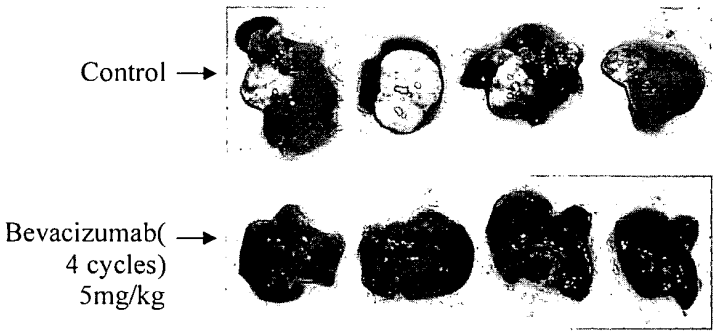


FIGURE 3D

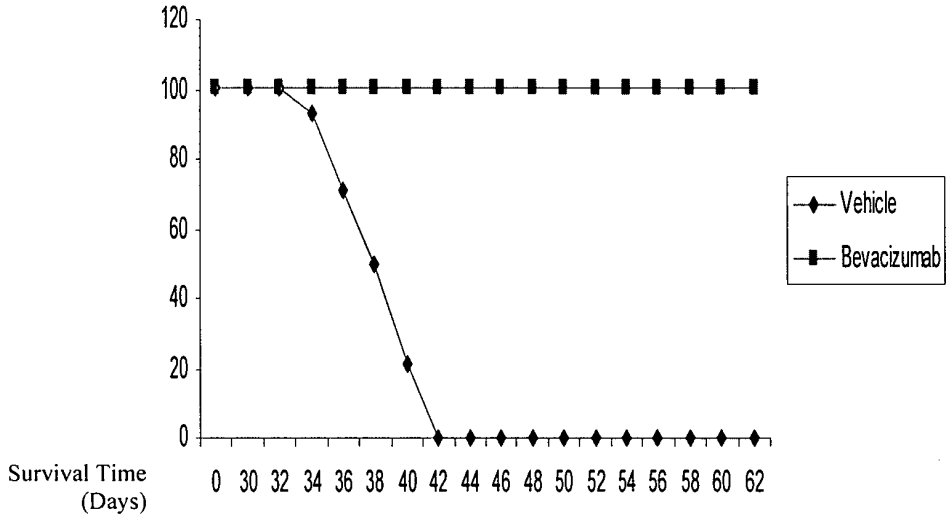

120
100
80
60
40
20
0
Survival Time (Days)
0 30 32 34 36 38 40 42 44 46 48 50 52 54 56 58 60 62
Vehicle
Bevacizumab

FIGURE 4

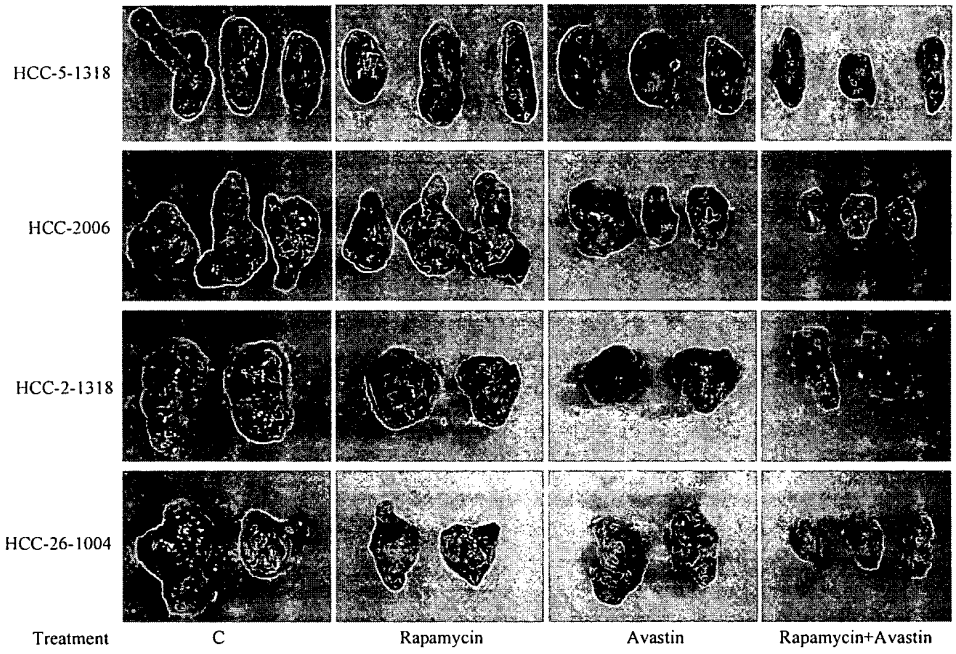
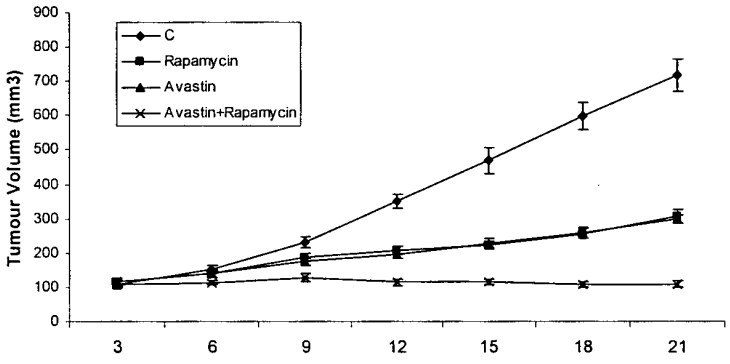

HCC-5-1318
HCC-2006
HCC-2-1318
HCC-26-1004
Treatment
C
Rapamycin
Avastin
Rapamycin+Avastin

FIGURE 5

HCC-26-1004

A



HCC-2-1318

B

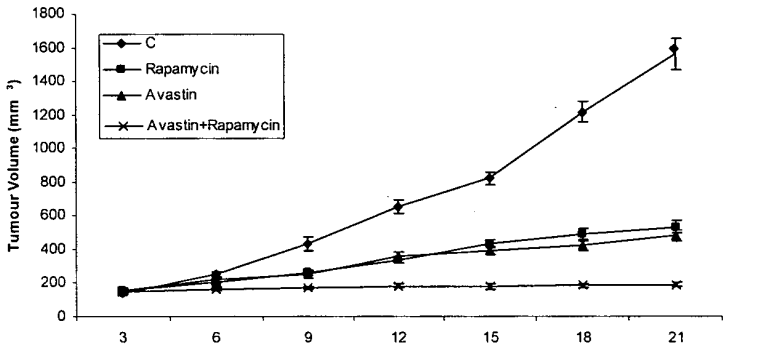
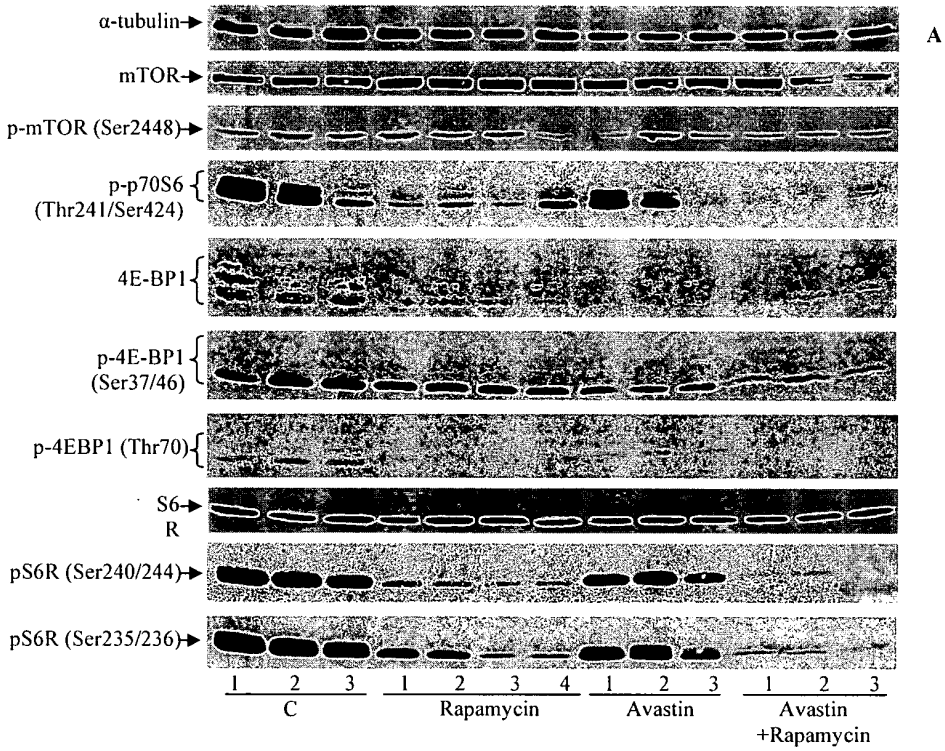


FIGURE 6


α-tubulin
mTOR
p-mTOR (Ser2448)
p-p70S6 (Thr241/Ser424)
4E-BP1
p-4E-BP1 (Ser37/46)
p-4EBP1 (Thr70)
S6R
pS6R (Ser240/244)
pS6R (Ser235/236)
A
1 2 3 1 2 3 4 1 2 3 1 2 3
C
Rapamycin
Avastin
Avastin +Rapamycin

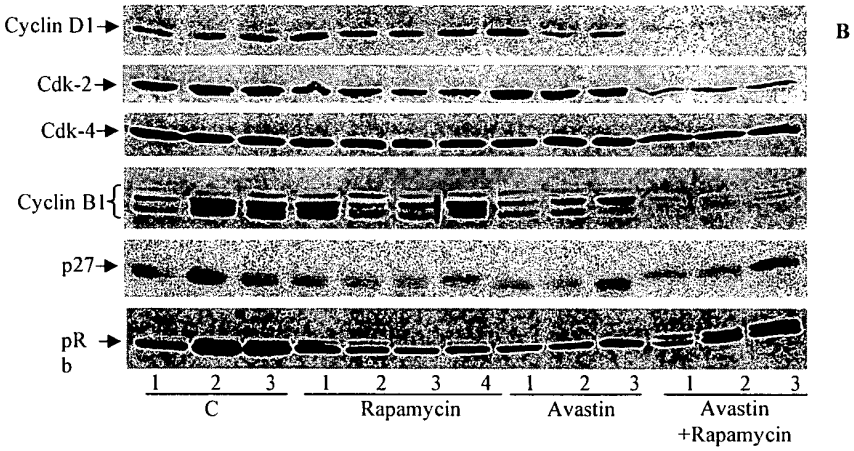
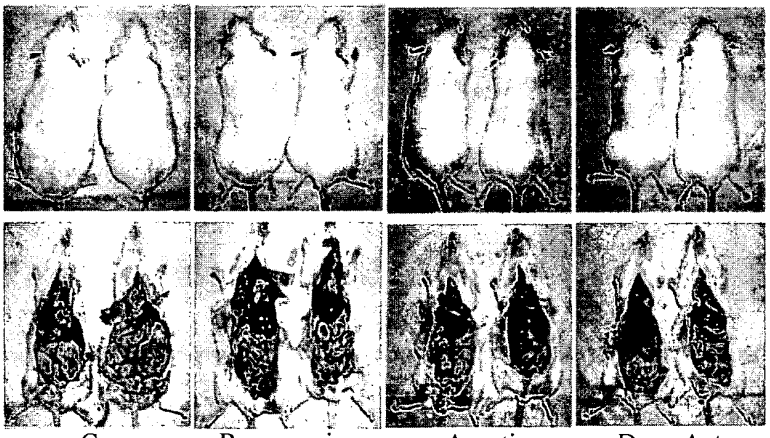

Cyclin D1
Cdk-2
Cdk-4
Cyclin B1
p27
pRb
B
1 2 3 1 2 3 4 1 2 3 1 2 3
C
Rapamycin
Avastin
Avastin +Rapamycin

FIGURE 7

HCC-26-1004 (Met)

A



C Rapamycin Avastin Drug A + Avastin

B



C Rapamycin Avastin Drug A +Avastin

C

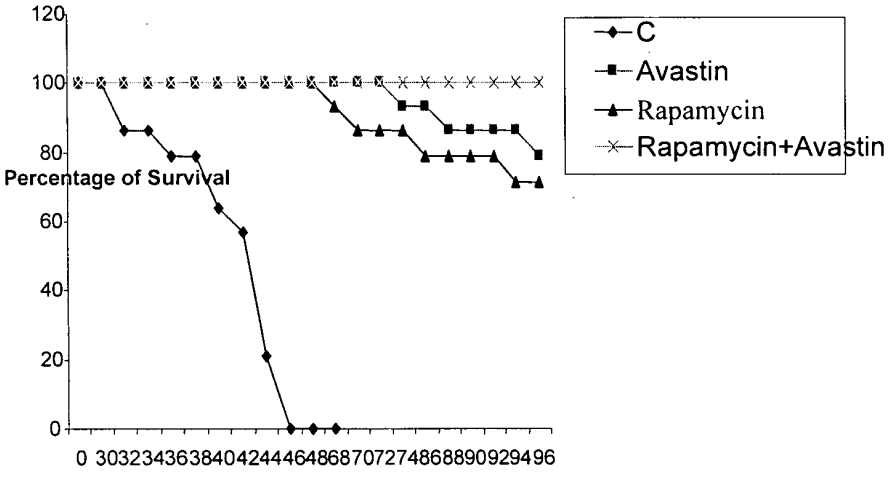
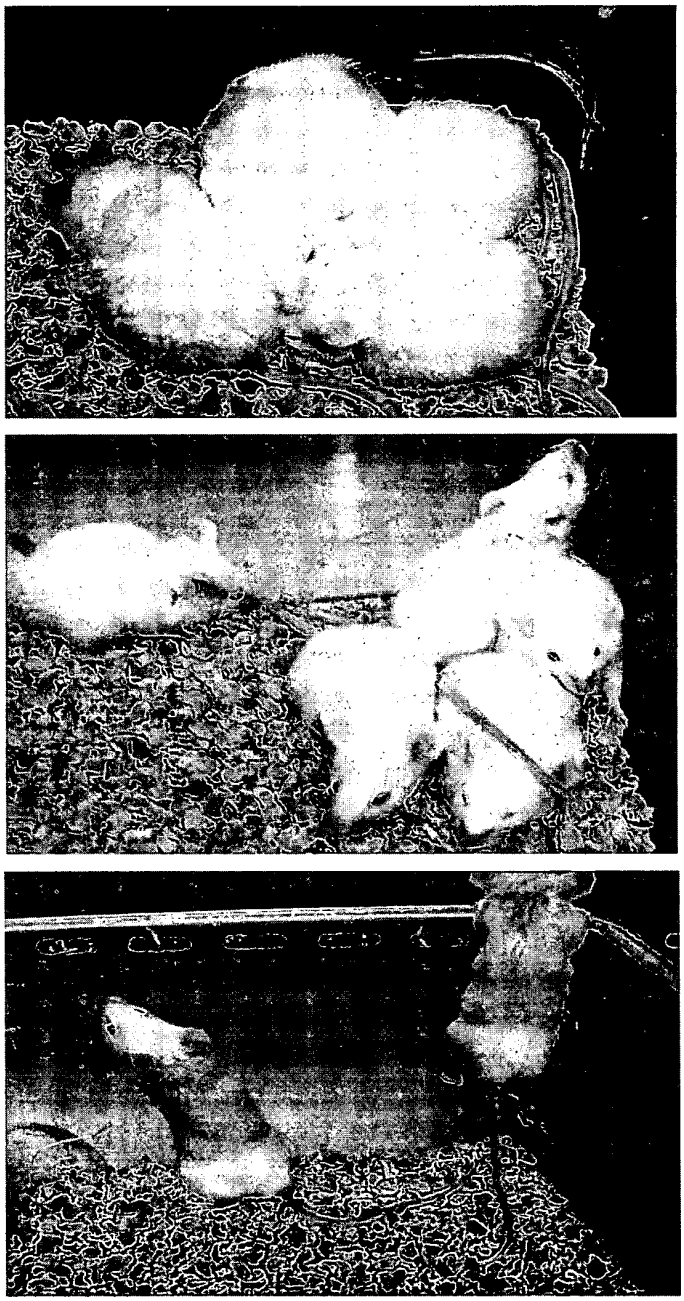


FIGURE 8



A

B

C

FIGURE 9

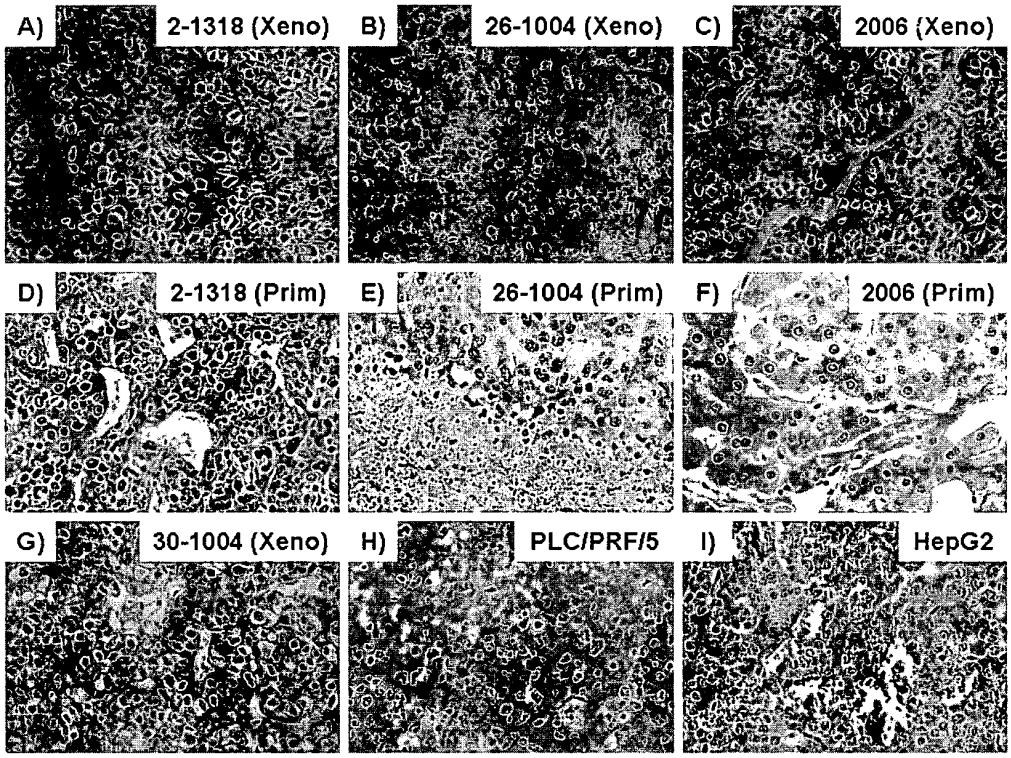

A)
2-1318 (Xeno)
B)
26-1004 (Xeno)
C)
2006 (Xeno)
D)
2-1318 (Prim)
E)
26-1004 (Prim)
F)
2006 (Prim)
G)
30-1004 (Xeno)
H)
PLC/PRF/5
I)
HepG2

FIGURE 10

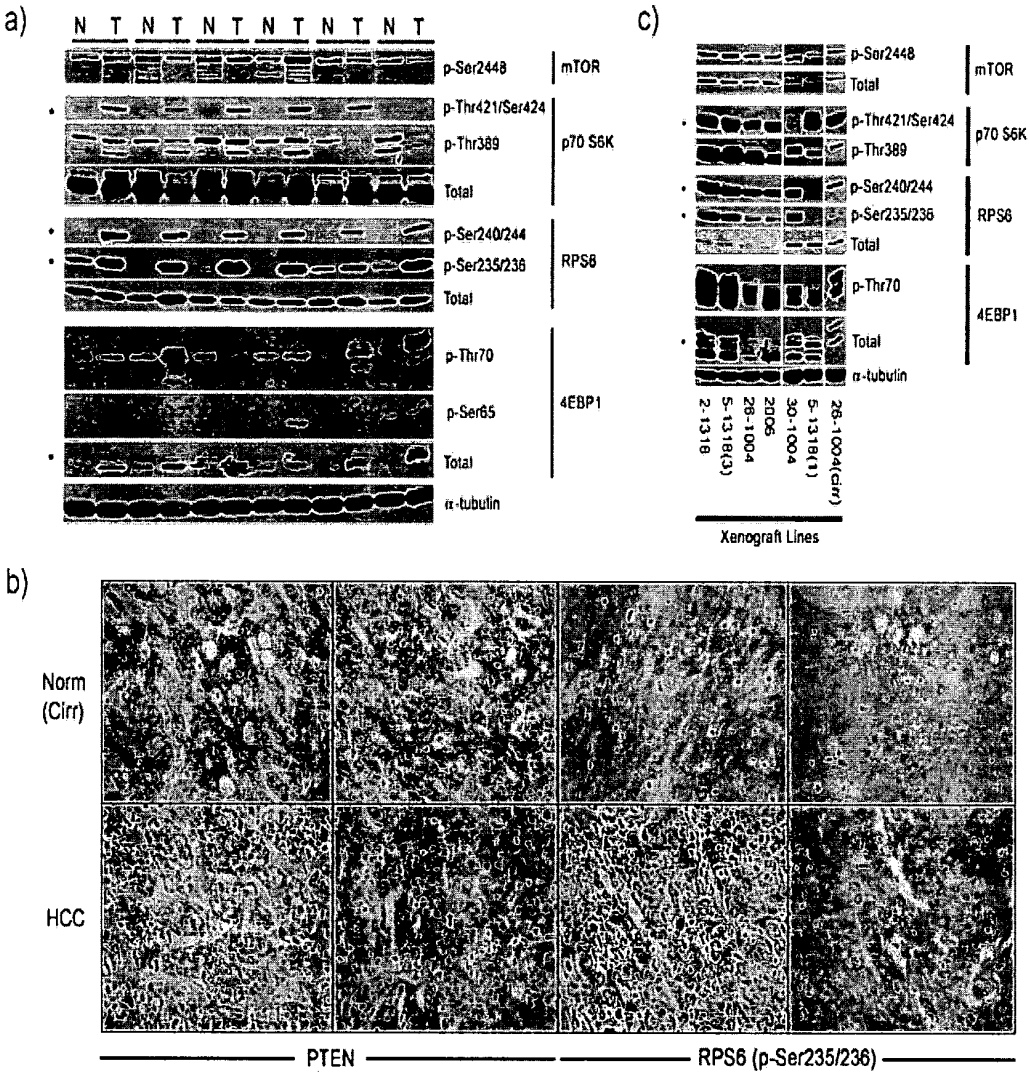

a)
N T N T N T N T N T N T
p-Ser2448
mTOR
p-Thr421/Ser424
p-Thr389
p70 S6K
Total
p-Ser240/244
p-Ser235/236
RPS6
Total
p-Thr70
p-Ser65
4EBP1
Total
α-tubulin
c)
p-Ser2448
Total
mTOR
p-Thr421/Ser424
p-Thr389
p70 S6K
p-Ser240/244
p-Ser235/236
RPS6
Total
p-Thr70
4EBP1
Total
α-tubulin
2-1318
5-1318(3)
28-1004
2006
30-1004
5-1318(1)
28-1004(cirr)
Xenograft Lines
b)
Norm (Cirr)
HCC
PTEN
RPS6 (p-Ser235/236)

FIGURE 11

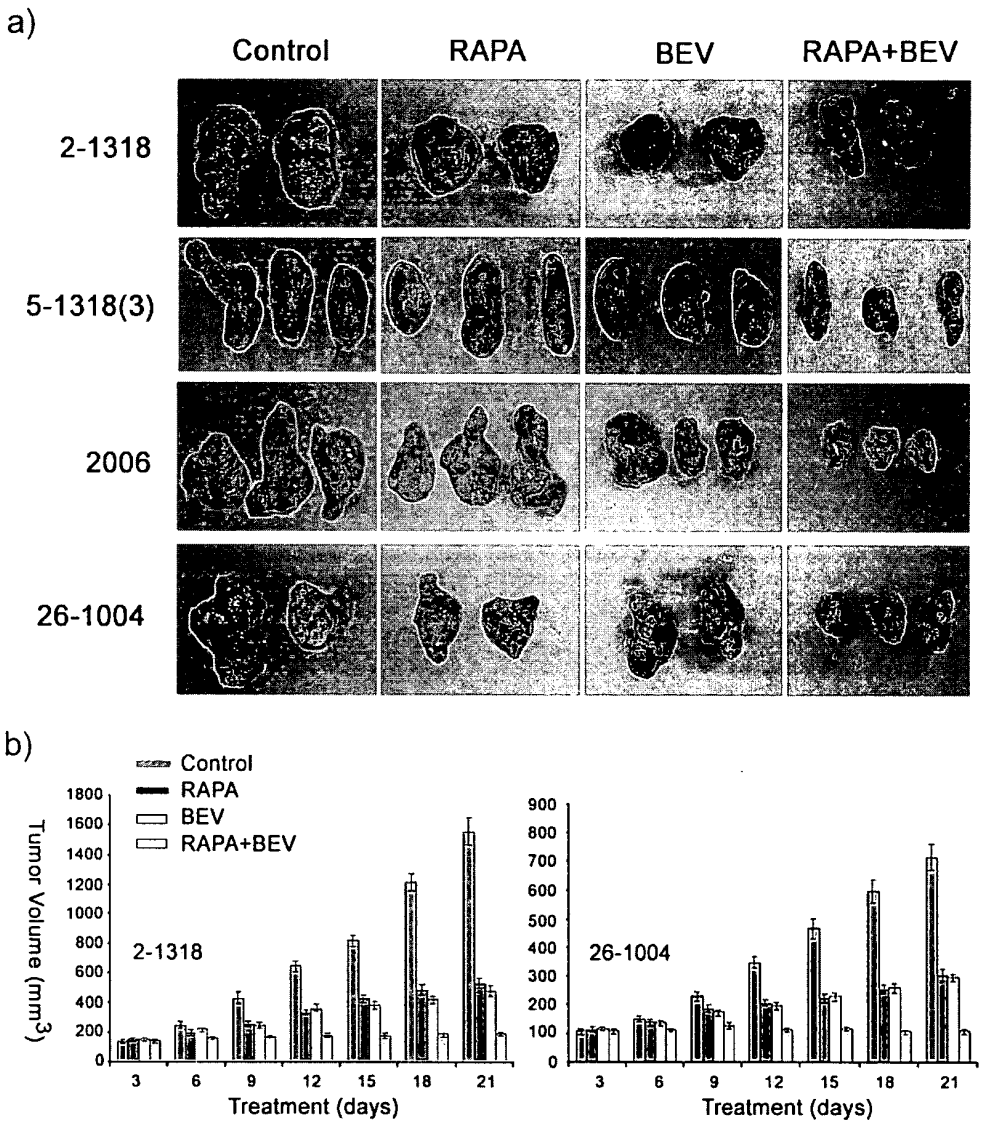

a)
Control
RAPA
BEV
RAPA+BEV
2-1318
5-1318(3)
2006
26-1004
b)
Control
RAPA
BEV
RAPA+BEV
Tumor Volume (mm3)
2-1318
26-1004
Treatment (days)
Treatment (days)

FIGURE 12

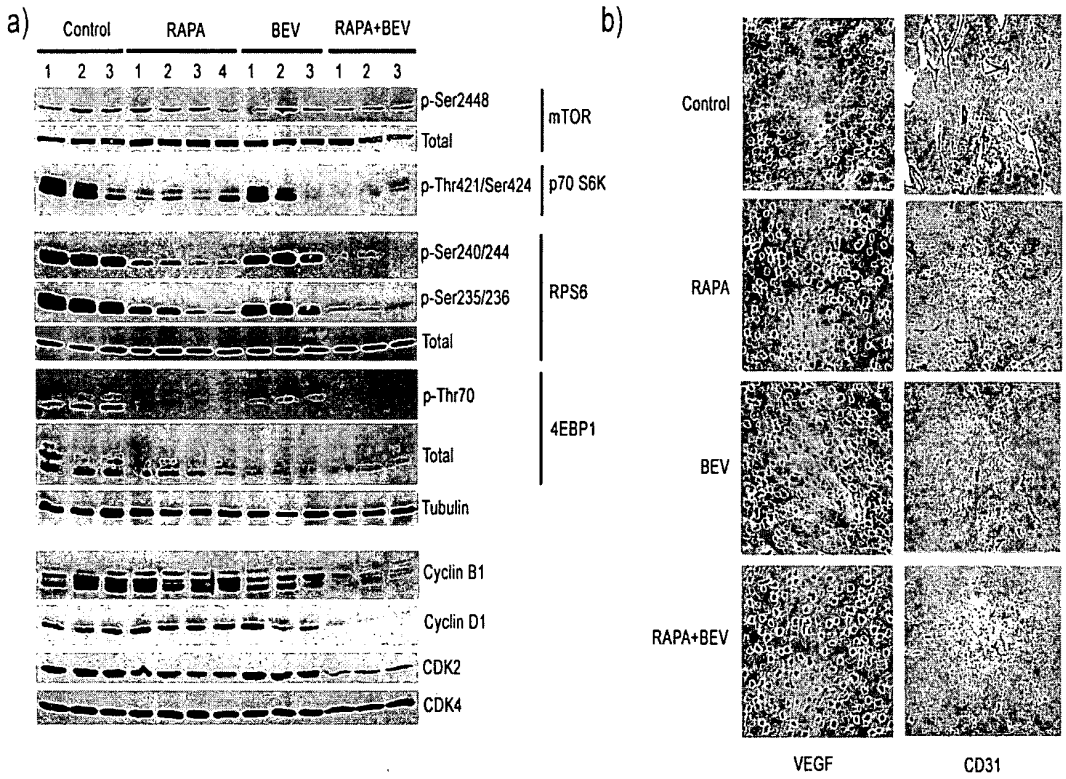

a)
Control
RAPA
BEV
RAPA+BEV
1 2 3 1 2 3 4 1 2 3 1 2 3
p-Ser2448
Total
mTOR
p-Thr421/Ser424
p70 S6K
p-Ser240/244
p-Ser235/236
Total
RPS6
p-Thr70
Total
4EBP1
Tubulin
Cyclin B1
Cyclin D1
CDK2
CDK4
b)
Control
RAPA
BEV
RAPA+BEV
VEGF
CD31

FIGURE 13

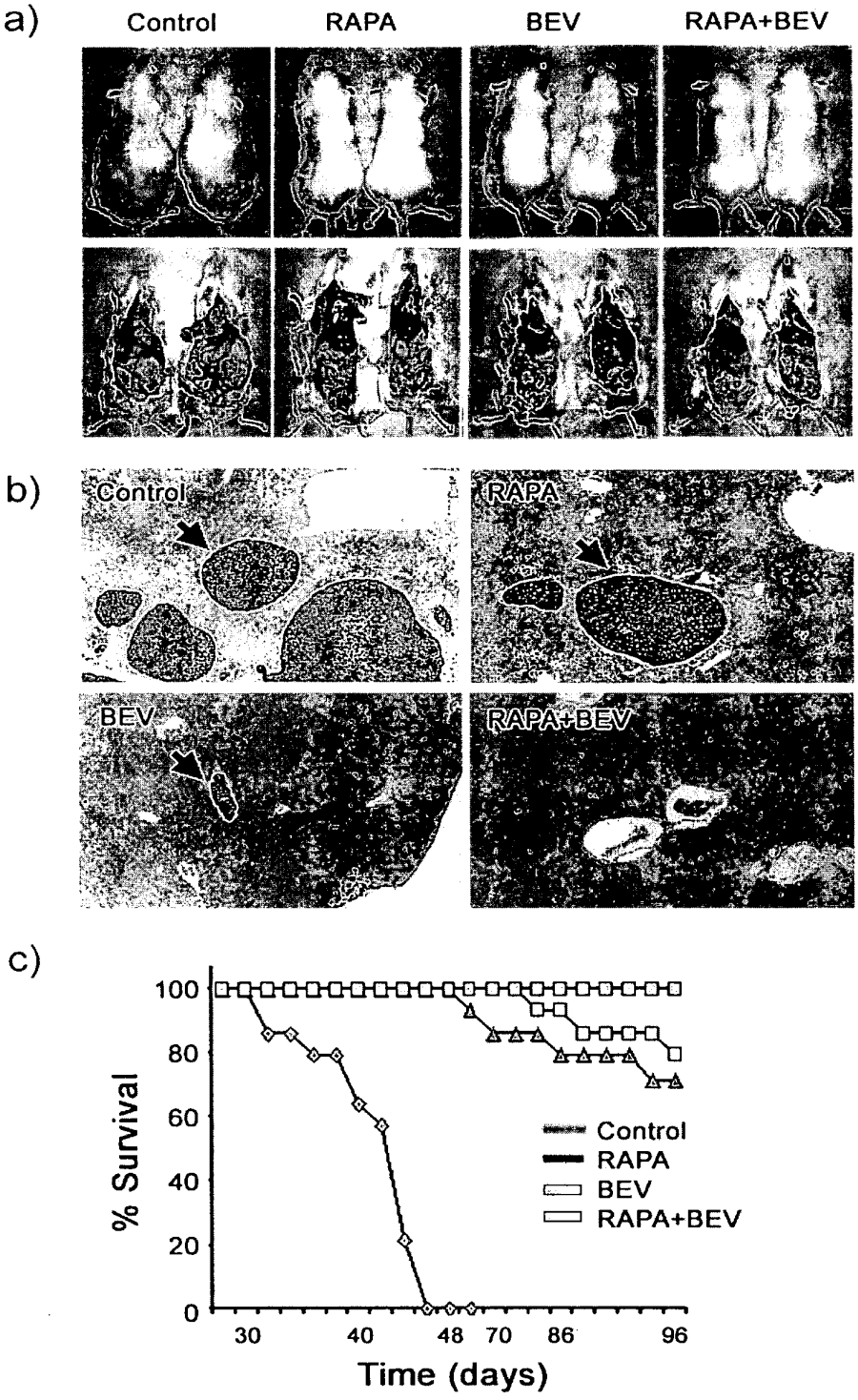
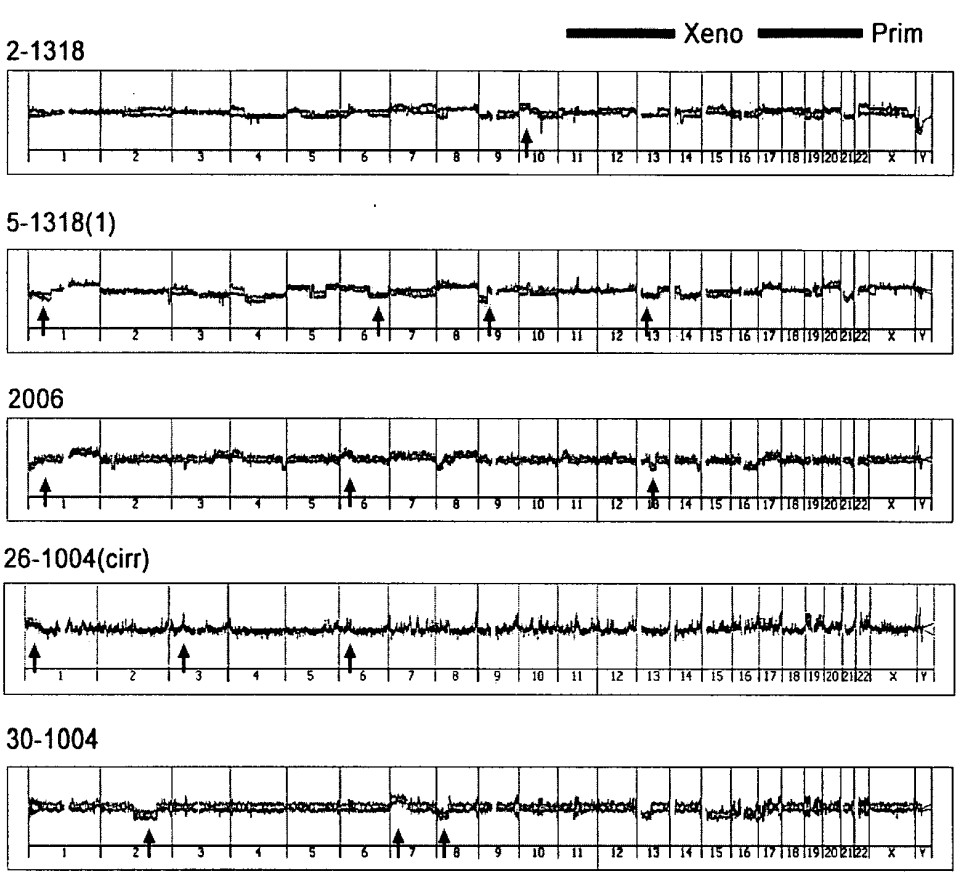

a)
Control
RAPA
BEV
RAPA+BEV
b)
Control
RAPA
BEV
RAPA+BEV
c)
% Survival
100
80
60
40
20
0
30
40
48
70
86
96
Time (days)
Control
RAPA
BEV
RAPA+BEV

FIGURE 14

a)


Xeno
Prim
2-1318
5-1318(1)
2006
26-1004(cirr)
30-1004

b)

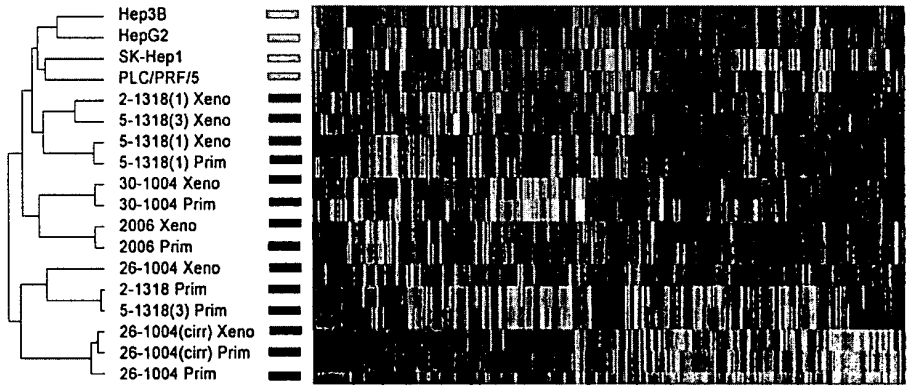

Hep3B
HepG2
SK-Hep1
PLC/PRF/5
2-1318(1) Xeno
5-1318(3) Xeno
5-1318(1) Xeno
5-1318(1) Prim
30-1004 Xeno
30-1004 Prim
2006 Xeno
2006 Prim
26-1004 Xeno
2-1318 Prim
5-1318(3) Prim
26-1004(cirr) Xeno
26-1004(cirr) Prim
26-1004 Prim

FIGURE 15

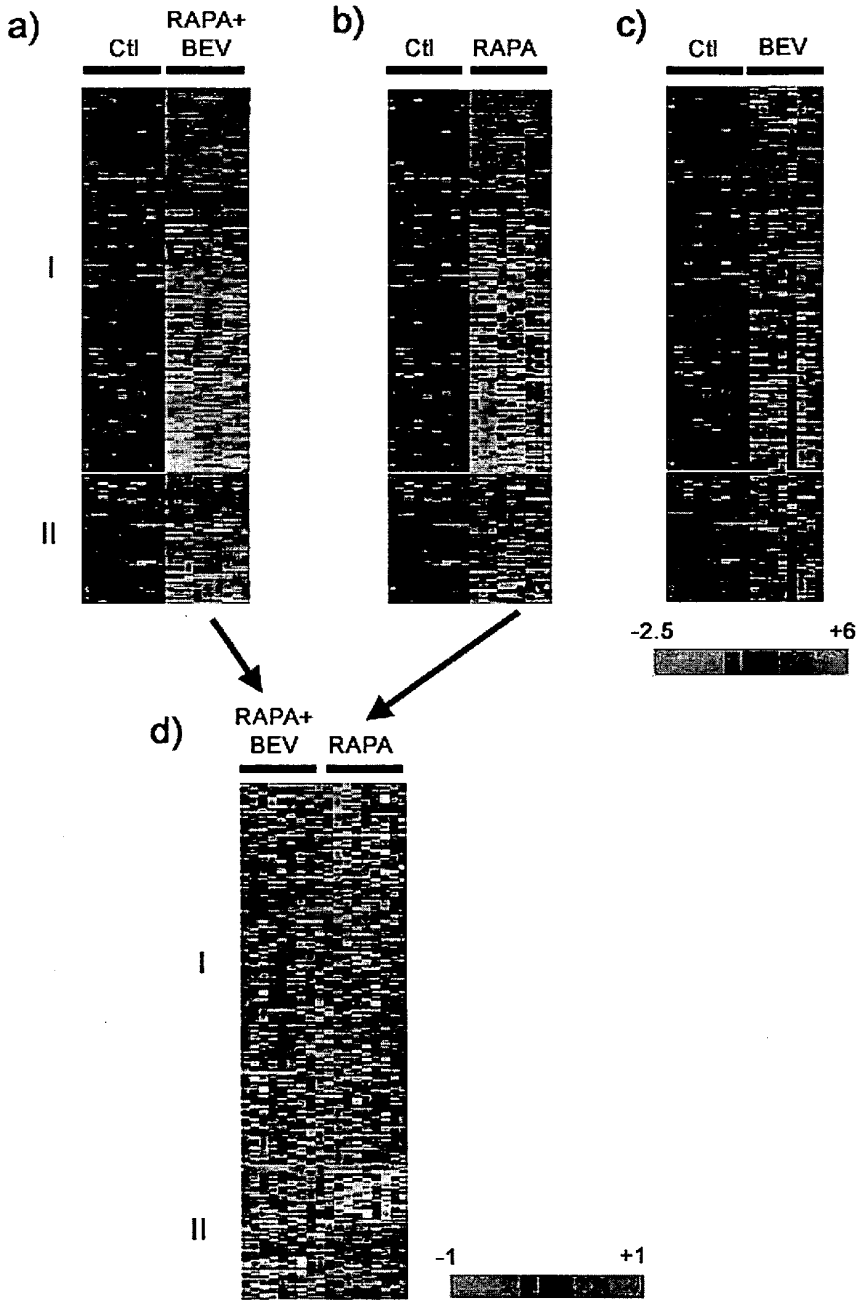
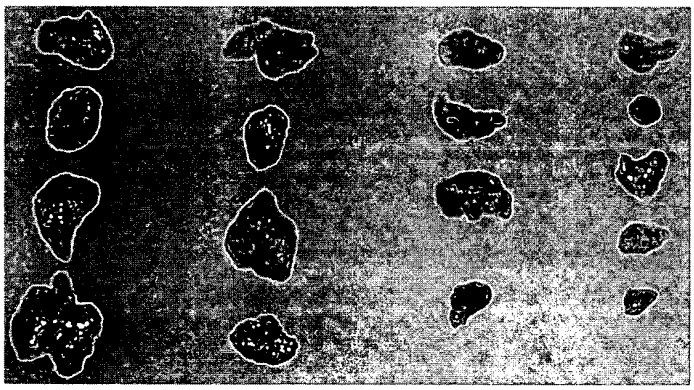


FIGURE 16

A



B

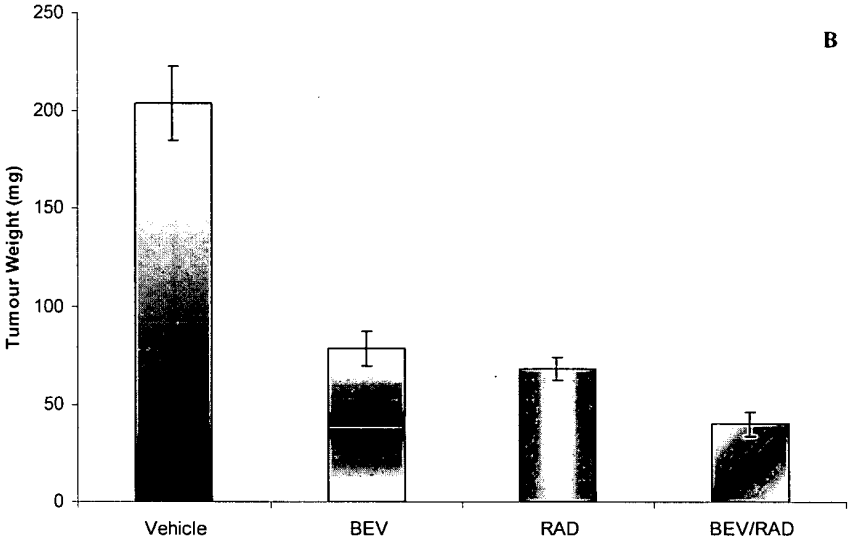


FIGURE 17

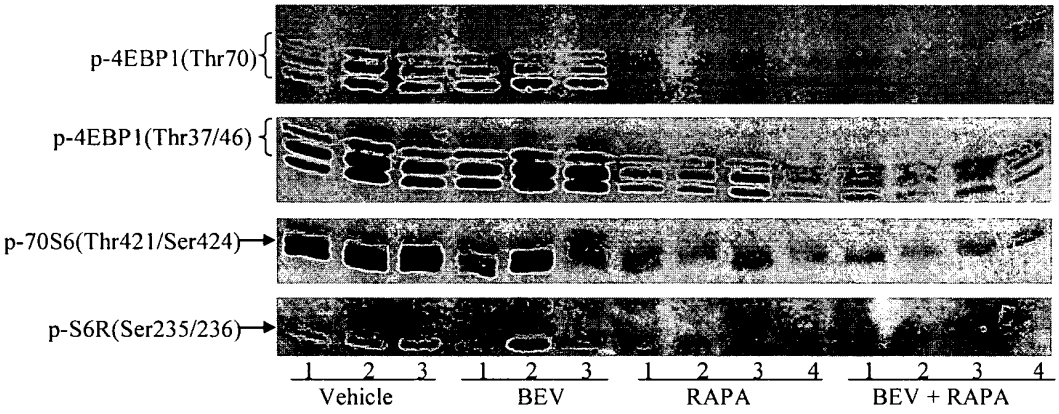
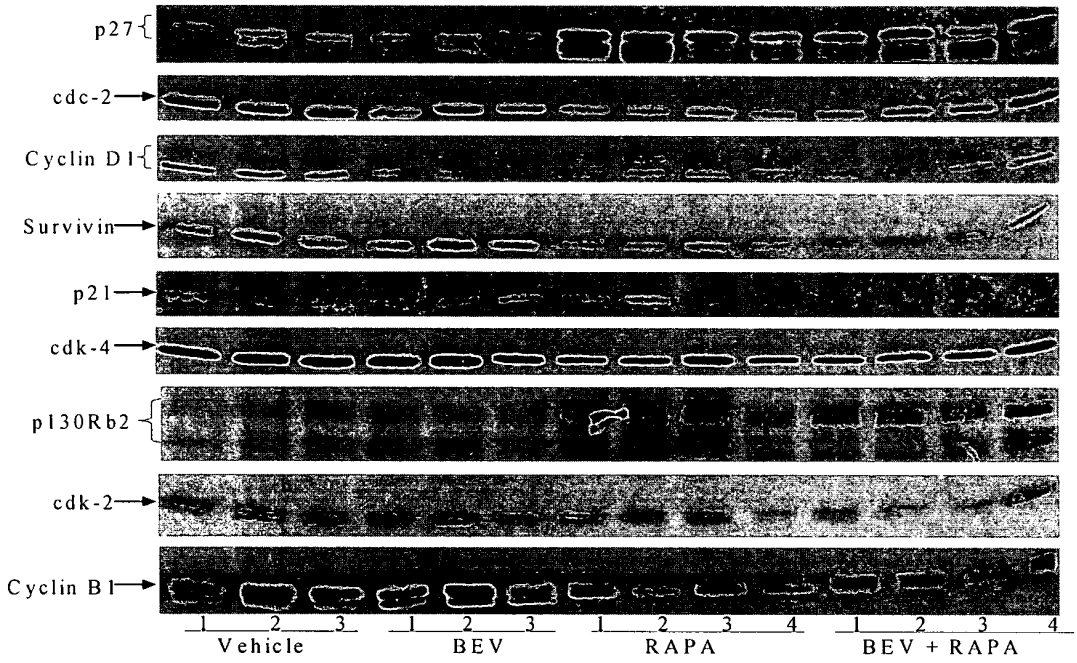

p-4EBP1(Thr70)
p-4EBP1(Thr37/46)
p-70S6(Thr421/Ser424)
p-S6R(Ser235/236)
1 2 3
1 2 3
1 2 3 4
1 2 3 4
Vehicle
BEV
RAPA
BEV + RAPA

FIGURE 18


p27
cdc-2
Cyclin D1
Survivin
p21
cdk-4
p130Rb2
cdk-2
Cyclin B1
1 2 3
1 2 3
1 2 3 4
1 2 3 4
Vehicle
BEV
RAPA
BEV + RAPA