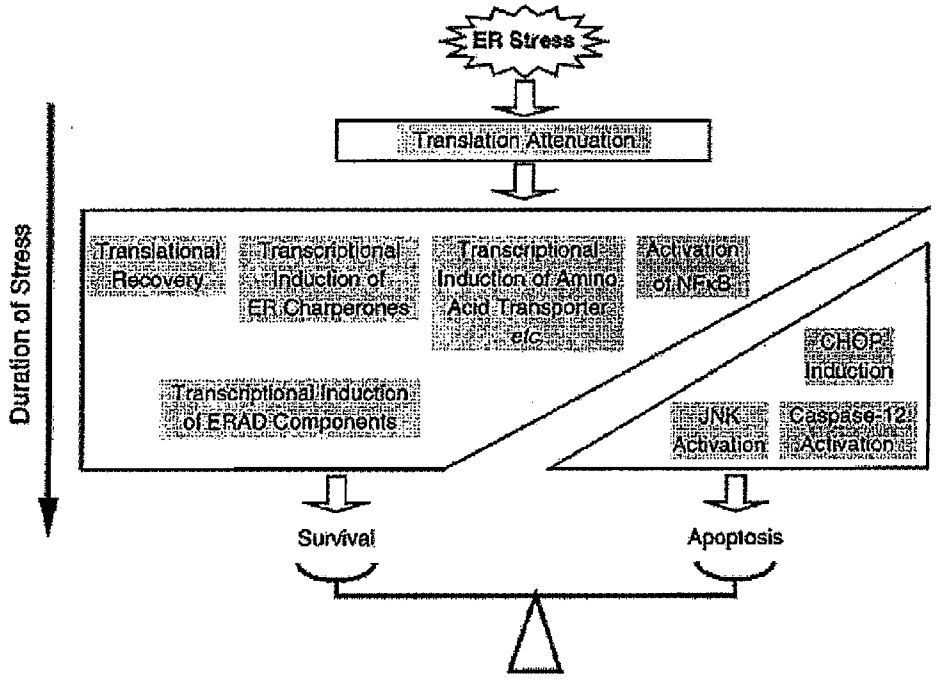

ER Stress
Translation Attenuation
Duration of Stress
Translational Recovery
Transcriptional Induction of ER Charperones
Transcriptional Induction of Amino Acid Transporter etc
Activation of NFκB
CHOP Induction
Transcriptional Induction of ERAD Components
JNK Activation
Caspase-12 Activation
Survival
Apoptosis

Figure 1

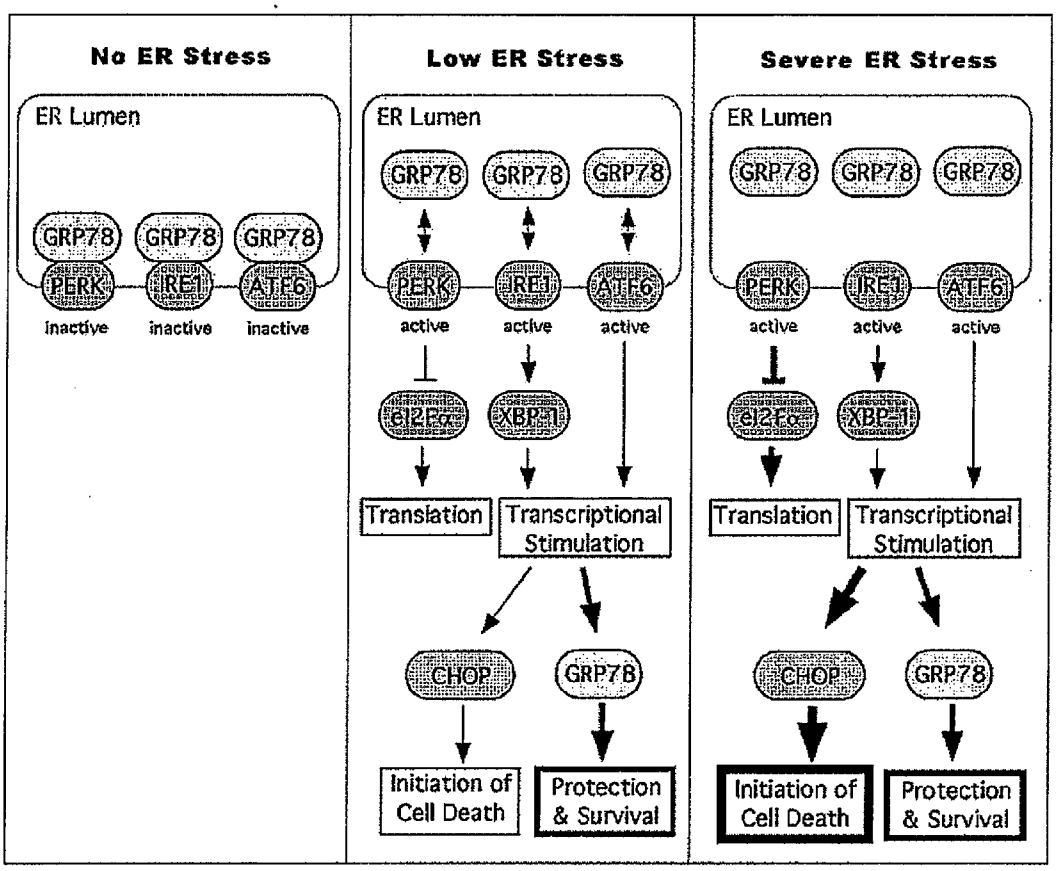

No ER Stress
ER Lumen
GRP78
GRP78
GRP78
PERK
IRE1
ATF6
inactive
inactive
inactive
Low ER Stress
ER Lumen
GRP78
GRP78
GRP78
PERK
IRE1
ATF6
active
active
active
eIF2α
XBP-1
Translation
Transcriptional Stimulation
CHOP
GRP78
Initiation of Cell Death
Protection & Survival
Severe ER Stress
ER Lumen
GRP78
GRP78
GRP78
PERK
IRE1
ATF6
active
active
active
eIF2α
XBP-1
Translation
Transcriptional Stimulation
CHOP
GRP78
Initiation of Cell Death
Protection & Survival

Figure 2

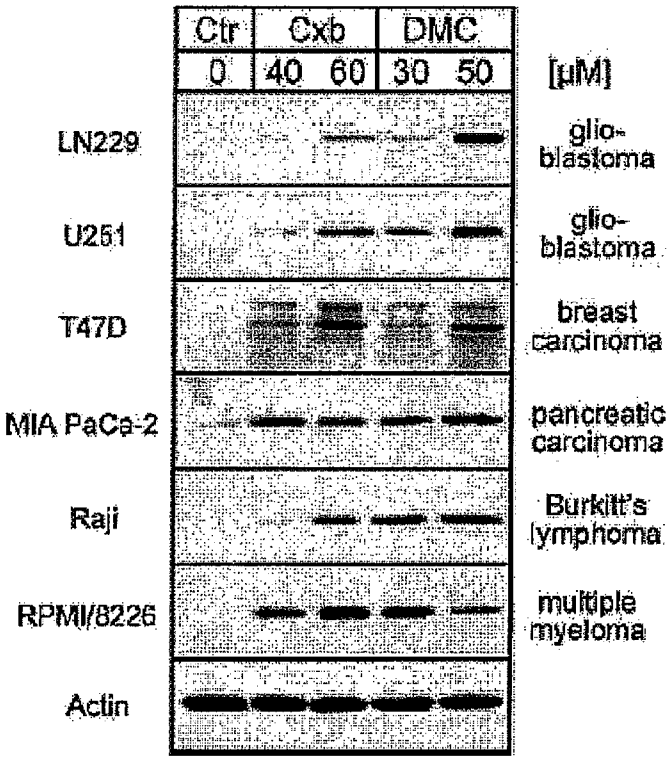

Ctr
Cxb
DMC
0
40
60
30
50
[μM]
LN229
glio-blastoma
U251
glio-blastoma
T47D
breast carcinoma
MIA PaCa-2
pancreatic carcinoma
Raji
Burkitt's lymphoma
RPMI/8226
multiple myeloma
Actin

Figure 3

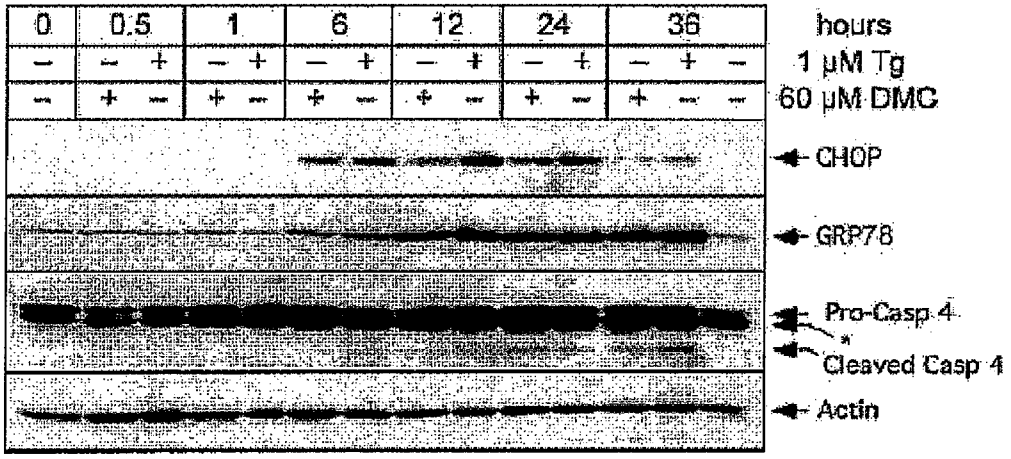

0
0.5
1
6
12
24
36
hours
1 μM Tg
60 μM DMC
CHOP
GRP78
Pro-Casp 4
Cleaved Casp 4
Actin

Figure 4

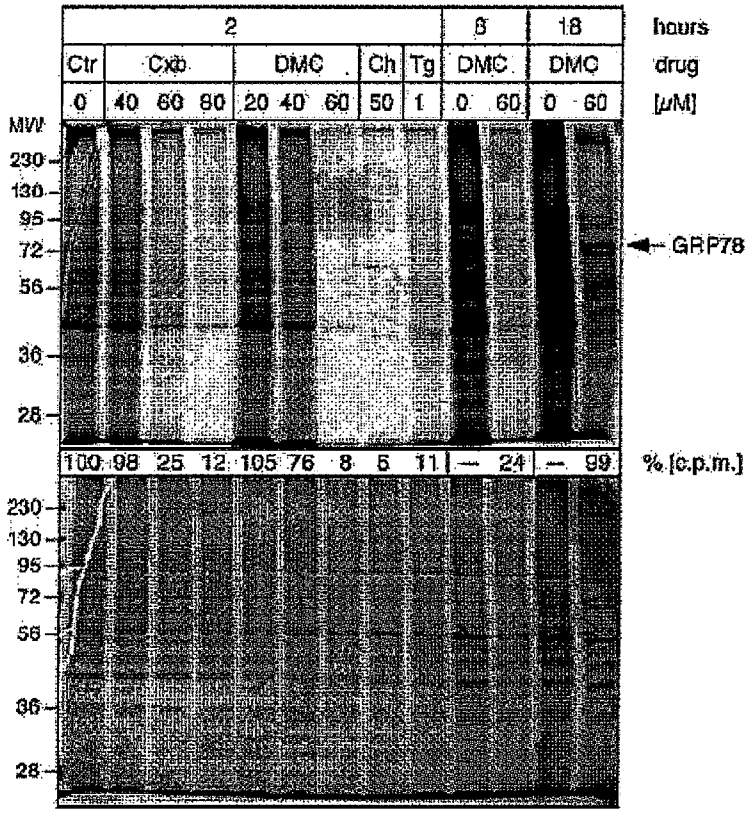

2
8
18
hours
Ctr
Cxb
DMC
Ch
Tg
DMC
DMC
drug
0
40 60 80
20 40 60
50
1
0 60
0 60
[μM]
MW
230
130
95
72
56
36
28
GRP78
100 98 25 12 105 76 8 5 11 — 24 — 99
% [c.p.m.]
230
130
95
72
56
36
28

Figure 5

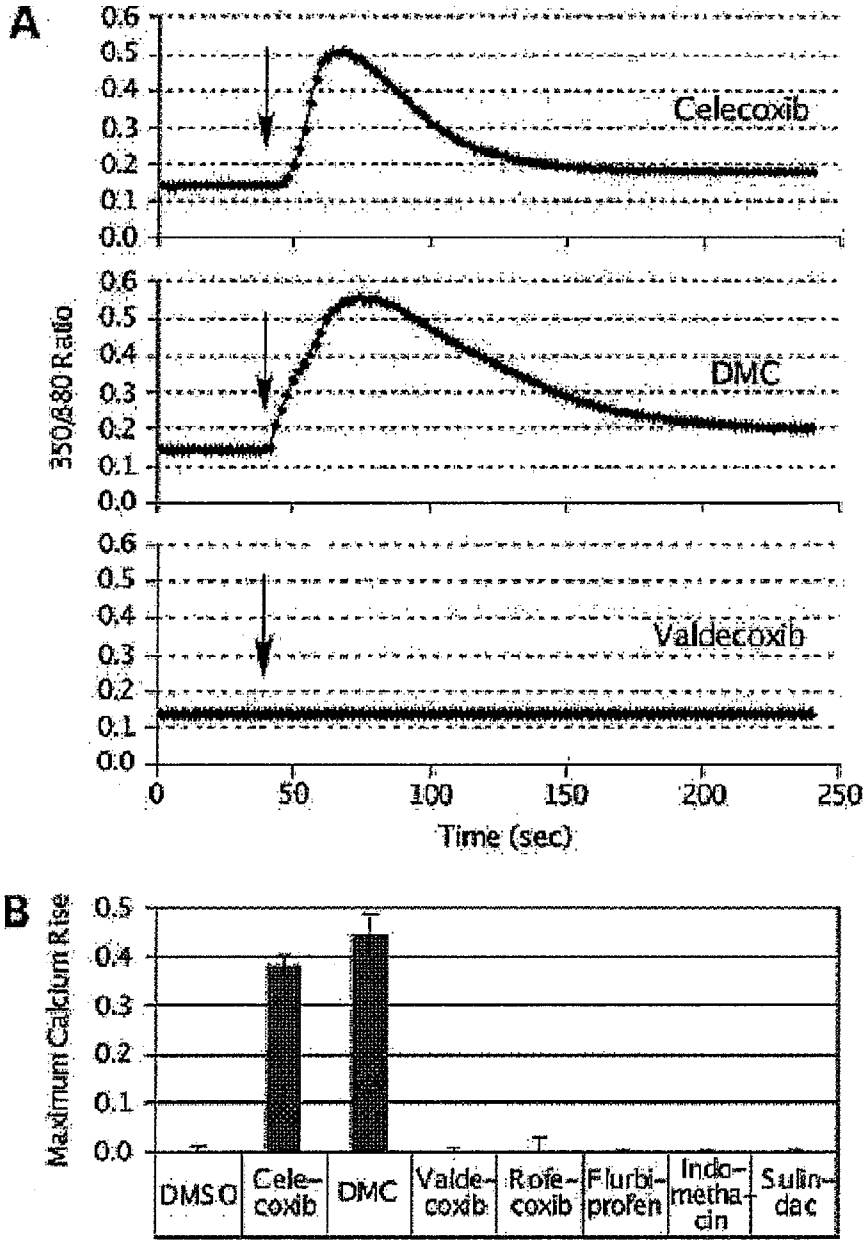

A
Celecoxib
DMC
Valdecoxib
350/380 Ratio
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
50
100
150
200
250
Time (sec)
B
Maximum Calcium Rise
0.5
0.4
0.3
0.2
0.1
0.0
DMSO
Cele-coxib
DMC
Valde-coxib
Rofe-coxib
Flurbi-profen
Indo-metha-cin
Sulin-dac

Figure 6

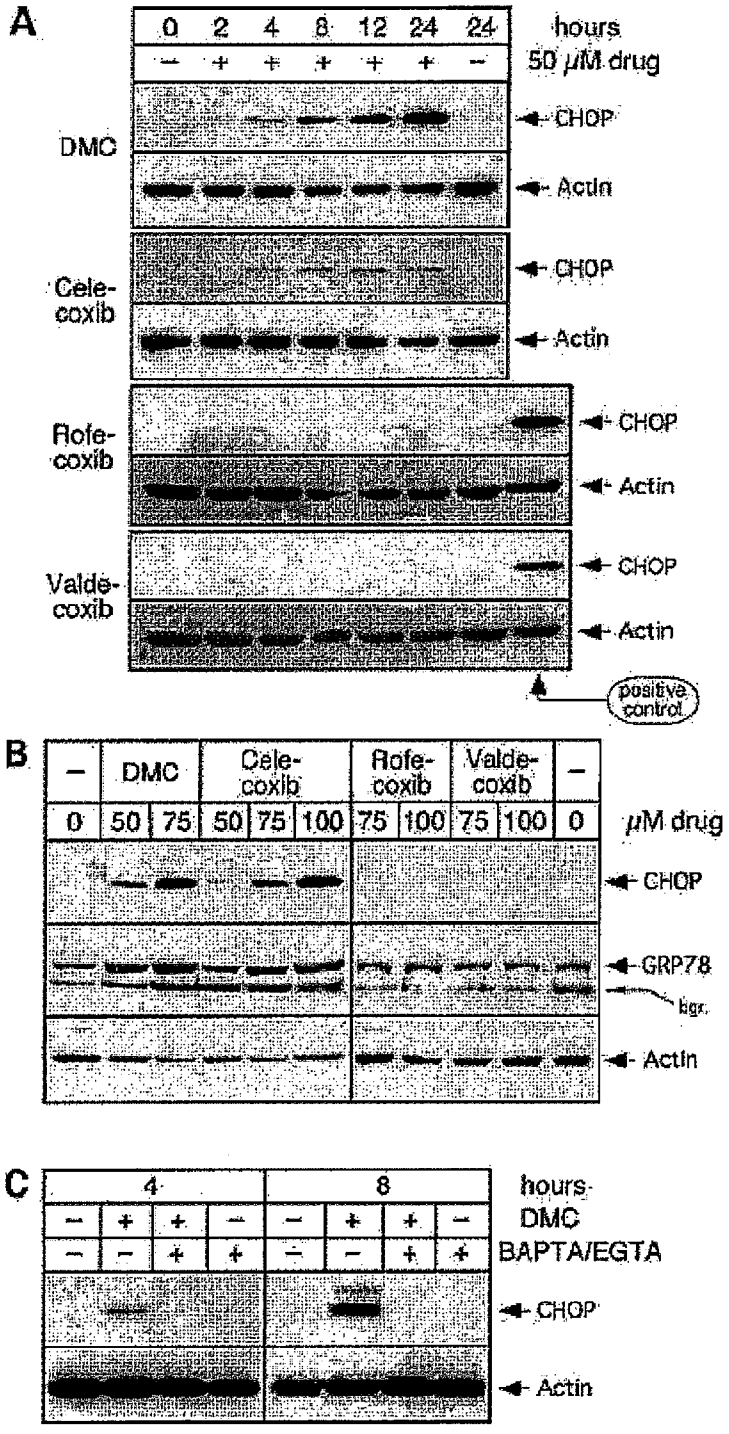

A
0 2 4 8 12 24 24
hours
– + + + + + –
50 μM drug
DMC
CHOP
Actin
Cele-coxib
CHOP
Actin
Rofe-coxib
CHOP
Actin
Valde-coxib
CHOP
Actin
positive control
B
– DMC Cele-coxib Rofe-coxib Valde-coxib –
0 50 75 50 75 100 75 100 75 100 0
μM drug
CHOP
GRP78
bgx.
Actin
C
4 8
hours
– + + – – + + –
DMC
– – + + – – + +
BAPTA/EGTA
CHOP
Actin

Figure 7

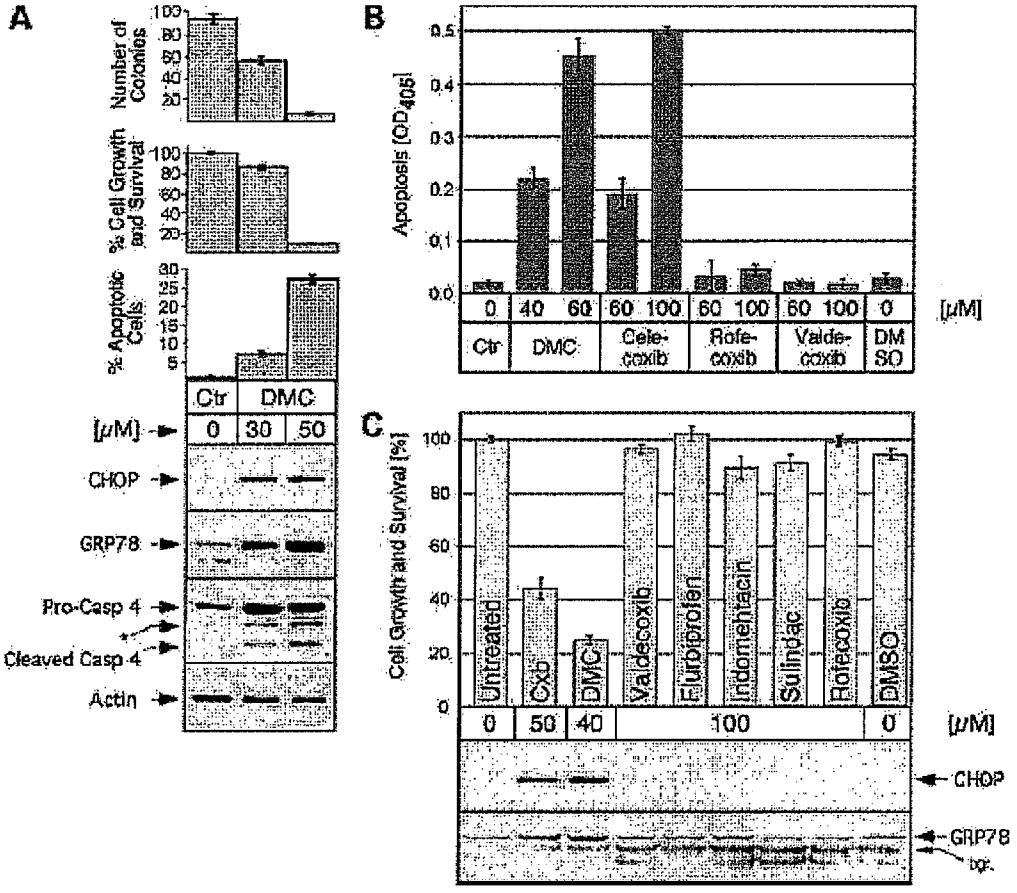

A
Number of Colonies
% Cell Growth and Survival
% Apoptotic Cells
Ctr
DMC
[μM]
0
30
50
CHOP
GRP78
Pro-Casp 4
Cleaved Casp 4
Actin
B
Apoptosis [OD405]
0
40
60
60
100
60
100
60
100
0
[μM]
Ctr
DMC
Cele-coxib
Rofe-coxib
Valde-coxib
DM SO
C
Cell Growth and Survival [%]
Untreated
Cxb
DMC
Valdecoxib
Flurbiprofen
Indomethacin
Sulindac
Rofecoxib
DMSO
0
50
40
100
0
[μM]
CHOP
GRP78
bgr.

Figure 8

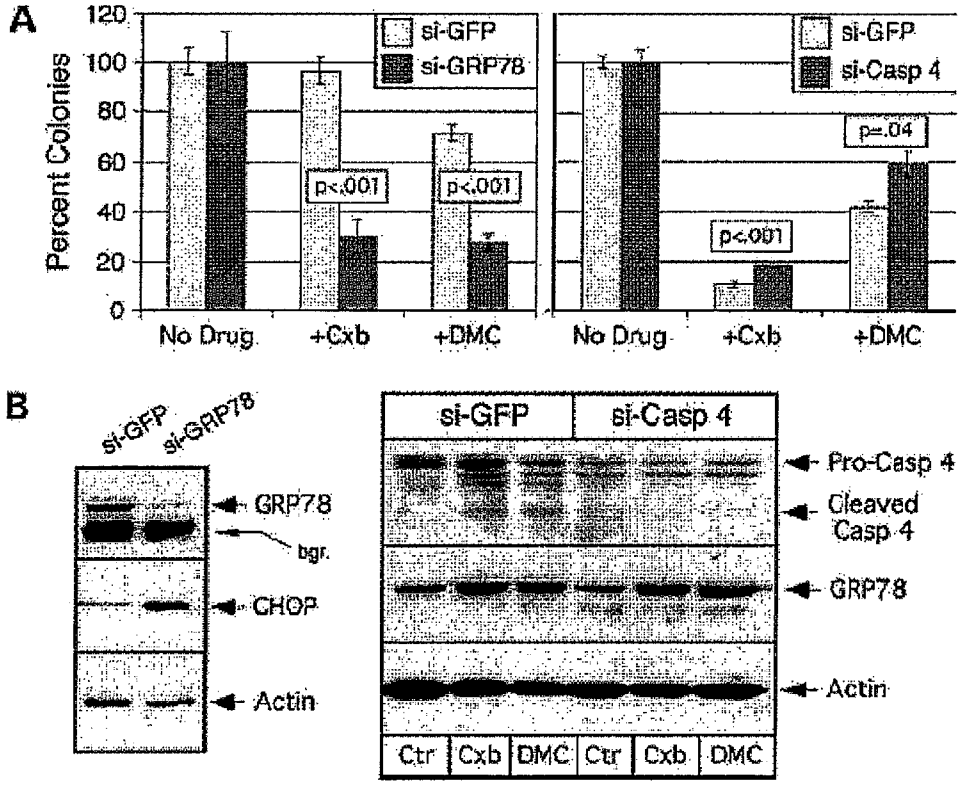

A
Percent Colonies
120
100
80
60
40
20
0
si-GFP
si-GRP78
p<.001
p<.001
No Drug
+Cxb
+DMC
si-GFP
si-Casp 4
p=.04
p<.001
No Drug
+Cxb
+DMC
B
si-GFP
si-GRP78
GRP78
bgr.
CHOP
Actin
si-GFP
si-Casp 4
Pro-Casp 4
Cleaved Casp 4
GRP78
Actin
Ctr
Cxb
DMC
Ctr
Cxb
DMC

Figure 9

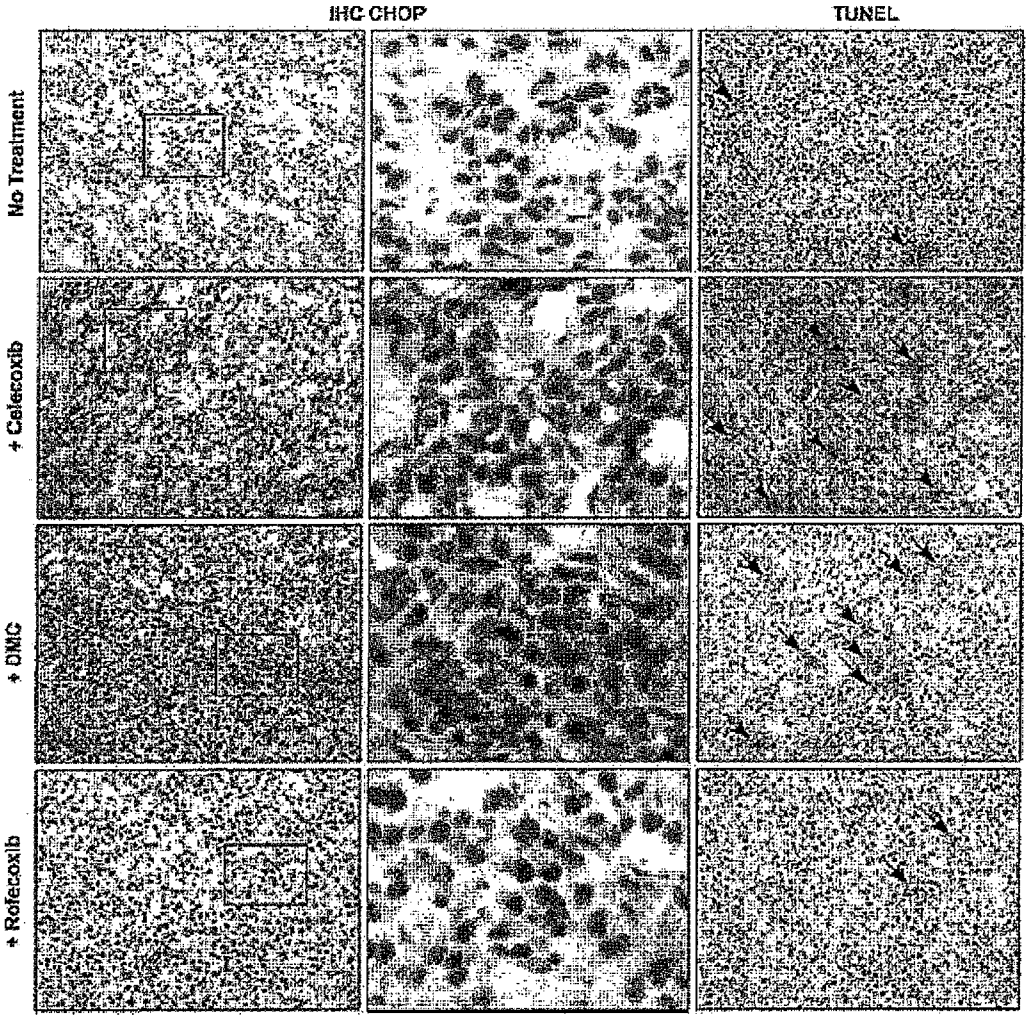


Figure 10

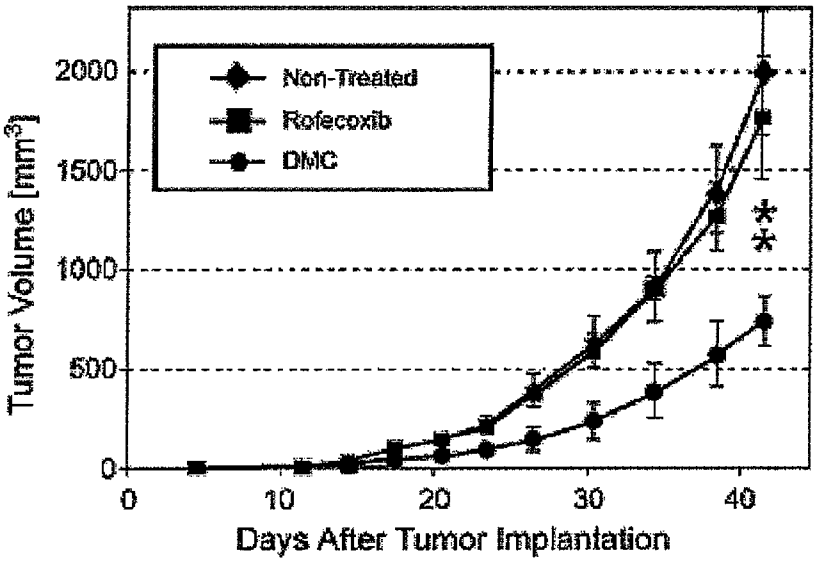

Non-Treated
Rofecoxib
DMC
Tumor Volume [mm3]
2000
1500
1000
500
0
0
10
20
30
40
Days After Tumor Implantation
**

Figure 11

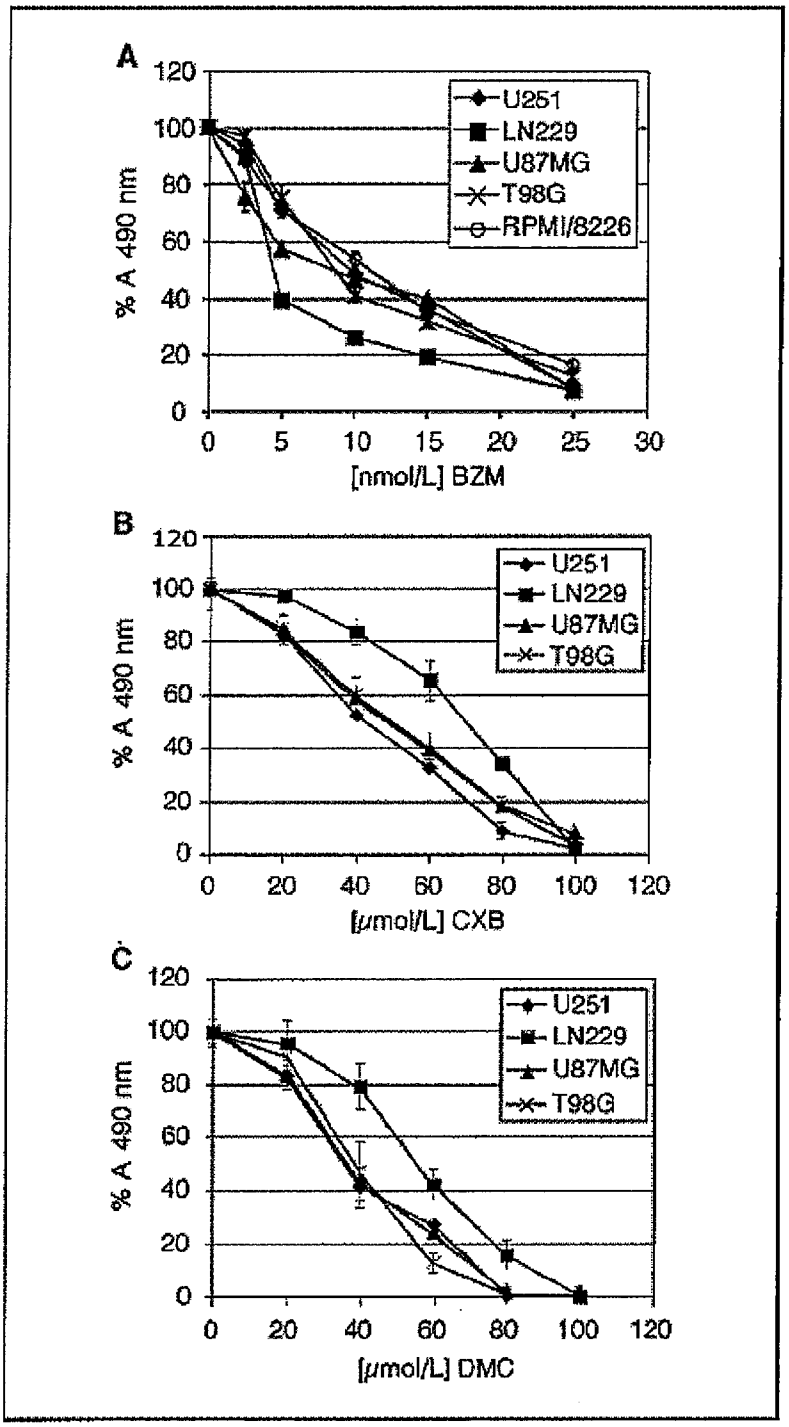

A
120
100
80
60
40
20
0
% A 490 nm
0 5 10 15 20 25 30
[nmol/L] BZM
U251
LN229
U87MG
T98G
RPMI/8226
B
120
100
80
60
40
20
0
% A 490 nm
0 20 40 60 80 100 120
[µmol/L] CXB
U251
LN229
U87MG
T98G
C
120
100
80
60
40
20
0
% A 490 nm
0 20 40 60 80 100 120
[µmol/L] DMC
U251
LN229
U87MG
T98G

Figure 12

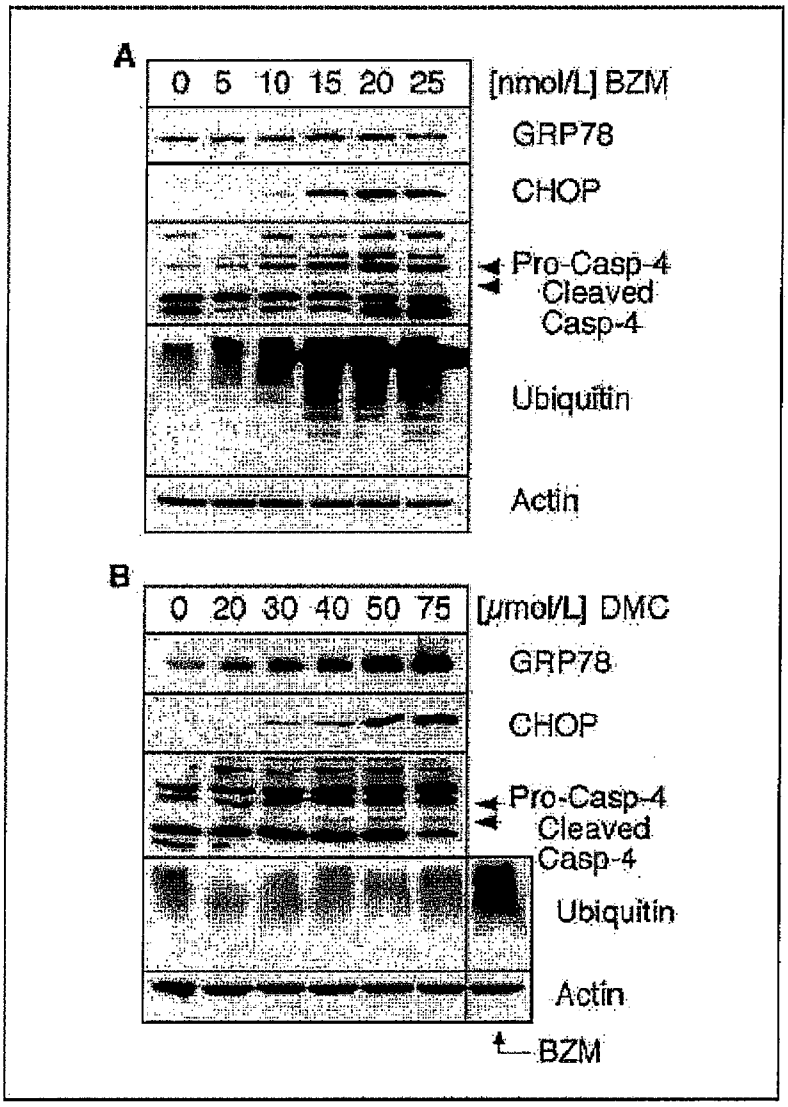

A
0 5 10 15 20 25
[nmol/L] BZM
GRP78
CHOP
Pro-Casp-4
Cleaved
Casp-4
Ubiquitin
Actin
B
0 20 30 40 50 75
[μmol/L] DMC
GRP78
CHOP
Pro-Casp-4
Cleaved
Casp-4
Ubiquitin
Actin
BZM

Figure 13

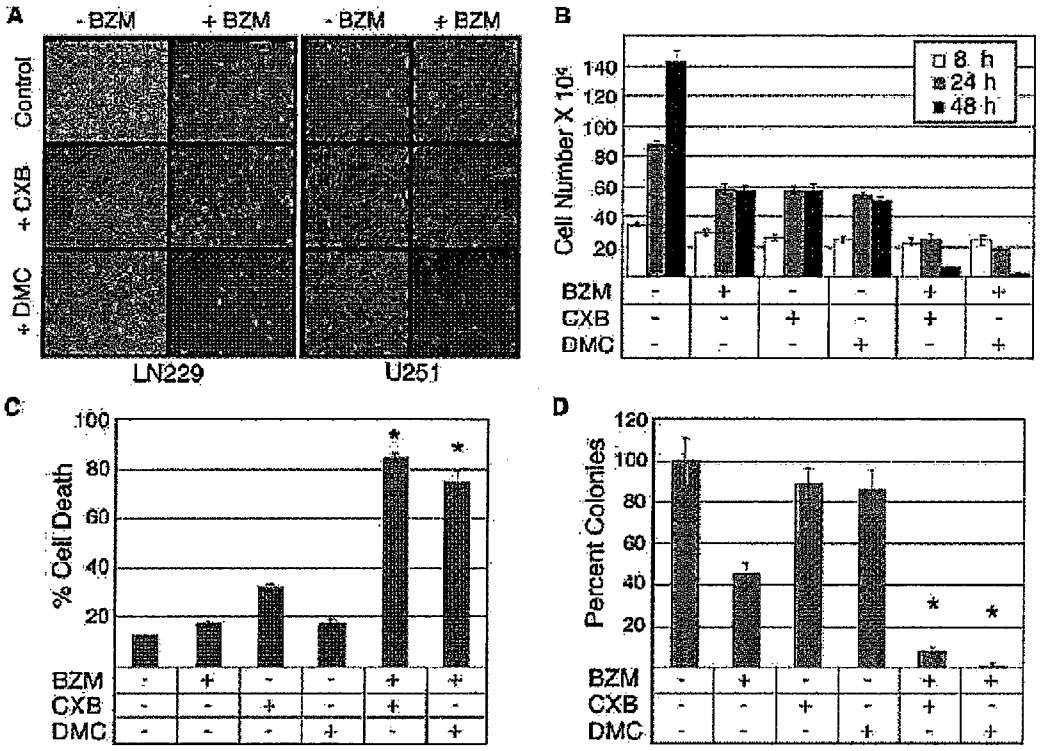

A
- BZM
+ BZM
- BZM
+ BZM
Control
+ CXB
+ DMC
LN229
U251
B
Cell Number X 10⁴
8 h
24 h
48 h
BZM
CXB
DMC
C
% Cell Death
D
Percent Colonies

Figure 14

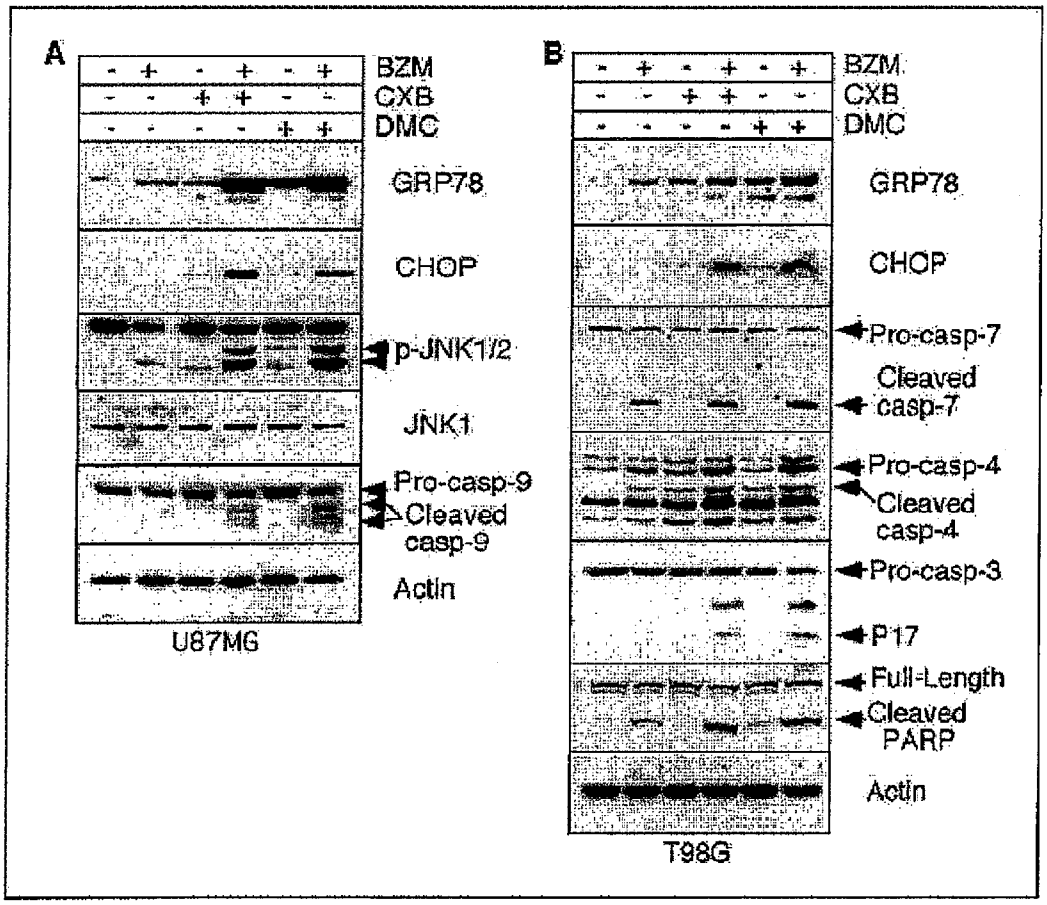

A
BZM
CXB
DMC
GRP78
CHOP
p-JNK1/2
JNK1
Pro-casp-9
Cleaved casp-9
Actin
U87MG
B
BZM
CXB
DMC
GRP78
CHOP
Pro-casp-7
Cleaved casp-7
Pro-casp-4
Cleaved casp-4
Pro-casp-3
P17
Full-Length
Cleaved PARP
Actin
T98G

Figure 15

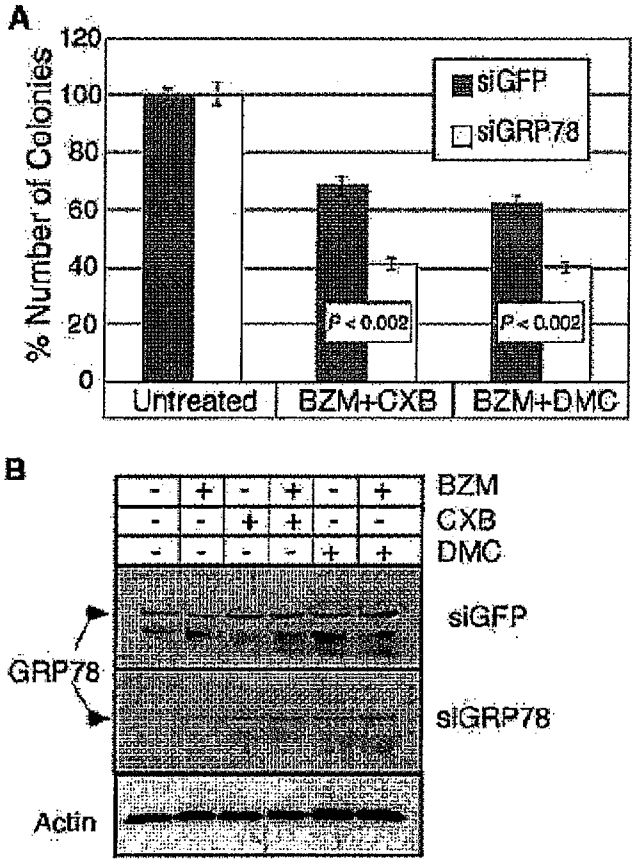

A
% Number of Colonies
120
100
80
60
40
20
0
siGFP
siGRP78
P < 0.002
P < 0.002
Untreated
BZM+CXB
BZM+DMC
B
BZM
CXB
DMC
siGFP
siGRP78
GRP78
Actin

Figure 16

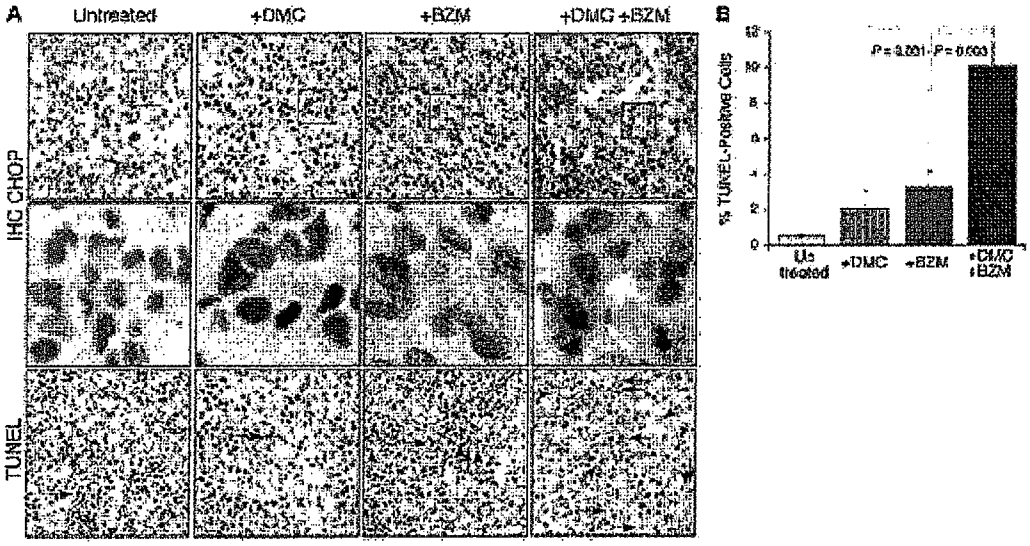

A
Untreated
+DMC
+BZM
+DMC +BZM
IHC CHOP
TUNEL
B
% TUNEL-Positive Cells
P = 0.001
P = 0.003
Untreated
+DMC
+BZM
+DMC +BZM

Figure 17

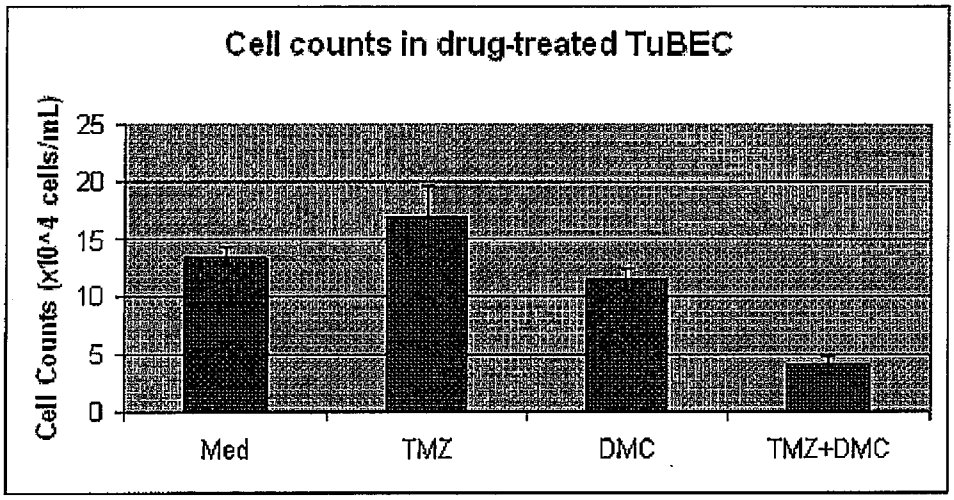

Cell counts in drug-treated TuBEC
Cell Counts (x10^4 cells/mL)
25
20
15
10
5
0
Med
TMZ
DMC
TMZ+DMC

Figure 18

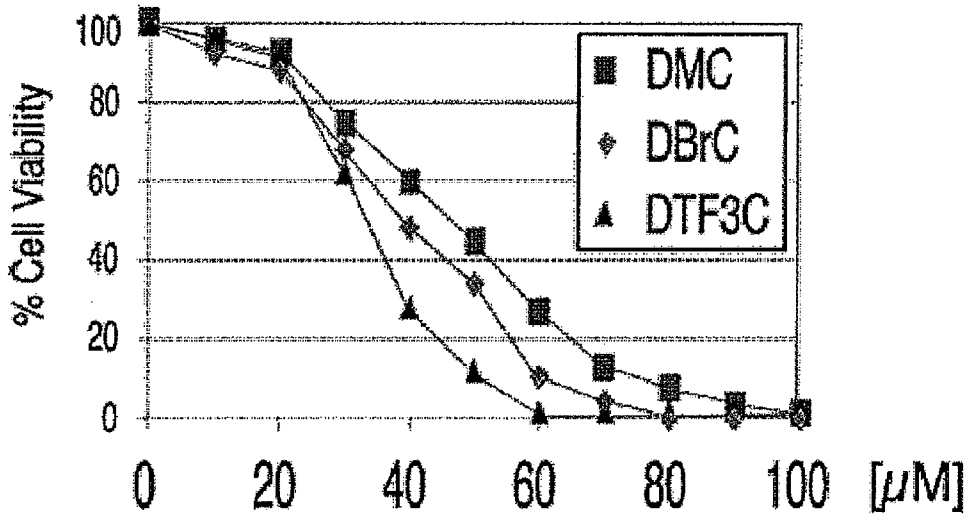

% Cell Viability
100
80
60
40
20
0
0
20
40
60
80
100
[μM]
DMC
DBrC
DTF3C

Figure 19