Phospho-AKT: a potential resistance marker to chemotherapy and therapy-target to restore sensitivity in pancreatic cancer

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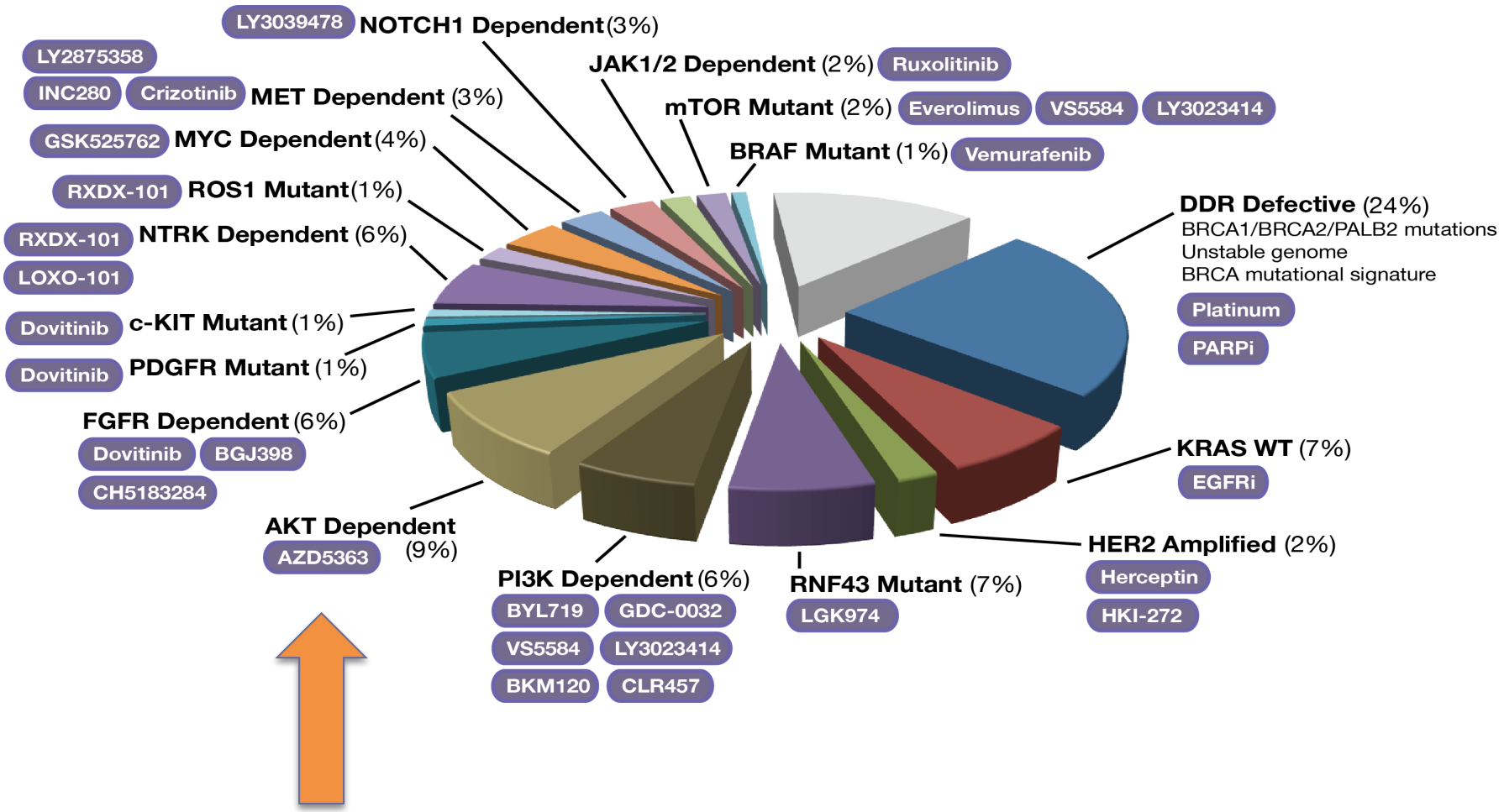
CONGRESSO CONGIUNTO DELLE SOCIETÀ SCIENTIFICHE ITALIANE DI CHIRURGIA
Sostenibilità, Innovazione, Contenzioso ed Etica: LE SFIDE DELLA CHIRURGIA

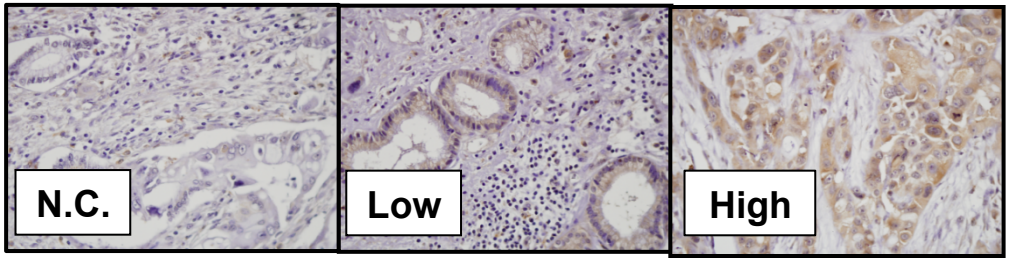
Pancreatic Cancer "Actionable Genome"



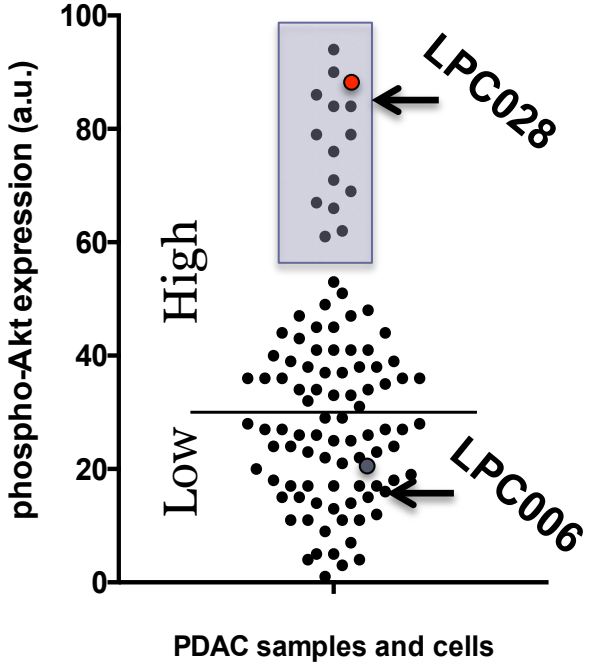
Bailey et al. Nature 2016

CLINICAL DATA

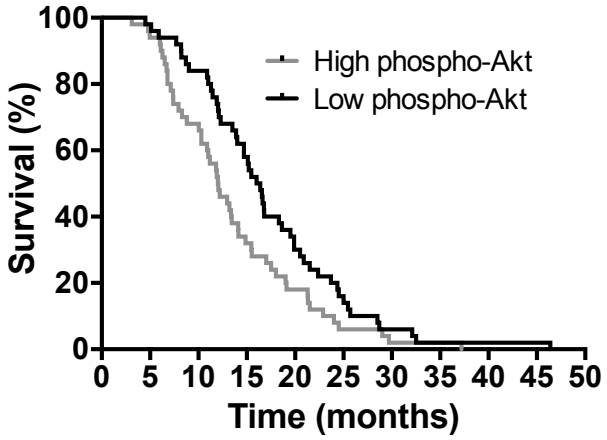
The protein expression of phospho-Akt was successfully evaluated by IHC in 100 human PDACs

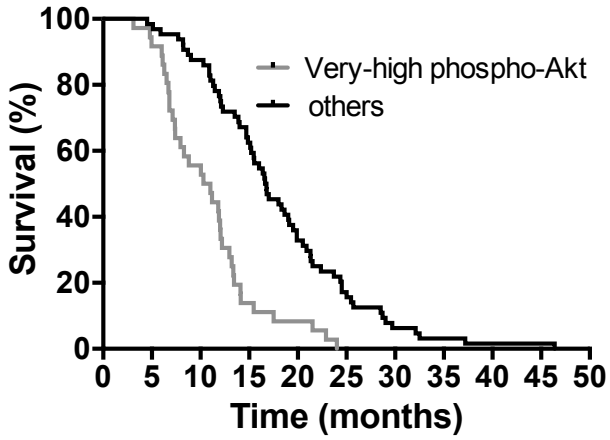


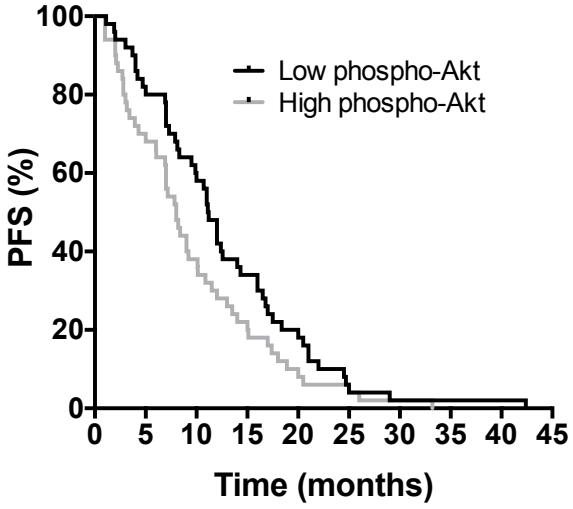
Patients were categorized according to their high vs. low phospho-Akt expression compared to the median value (30 a.u.)

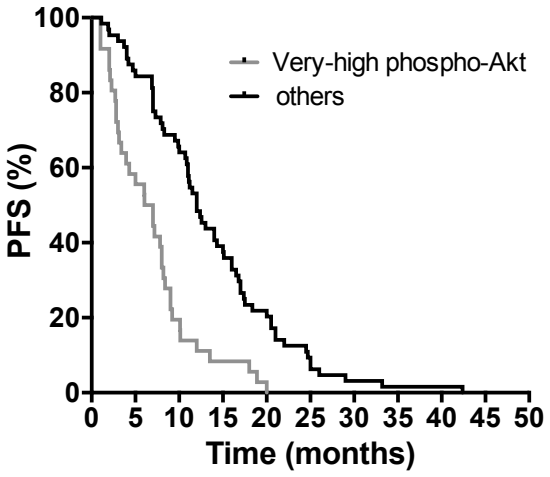


CLINICAL DATA

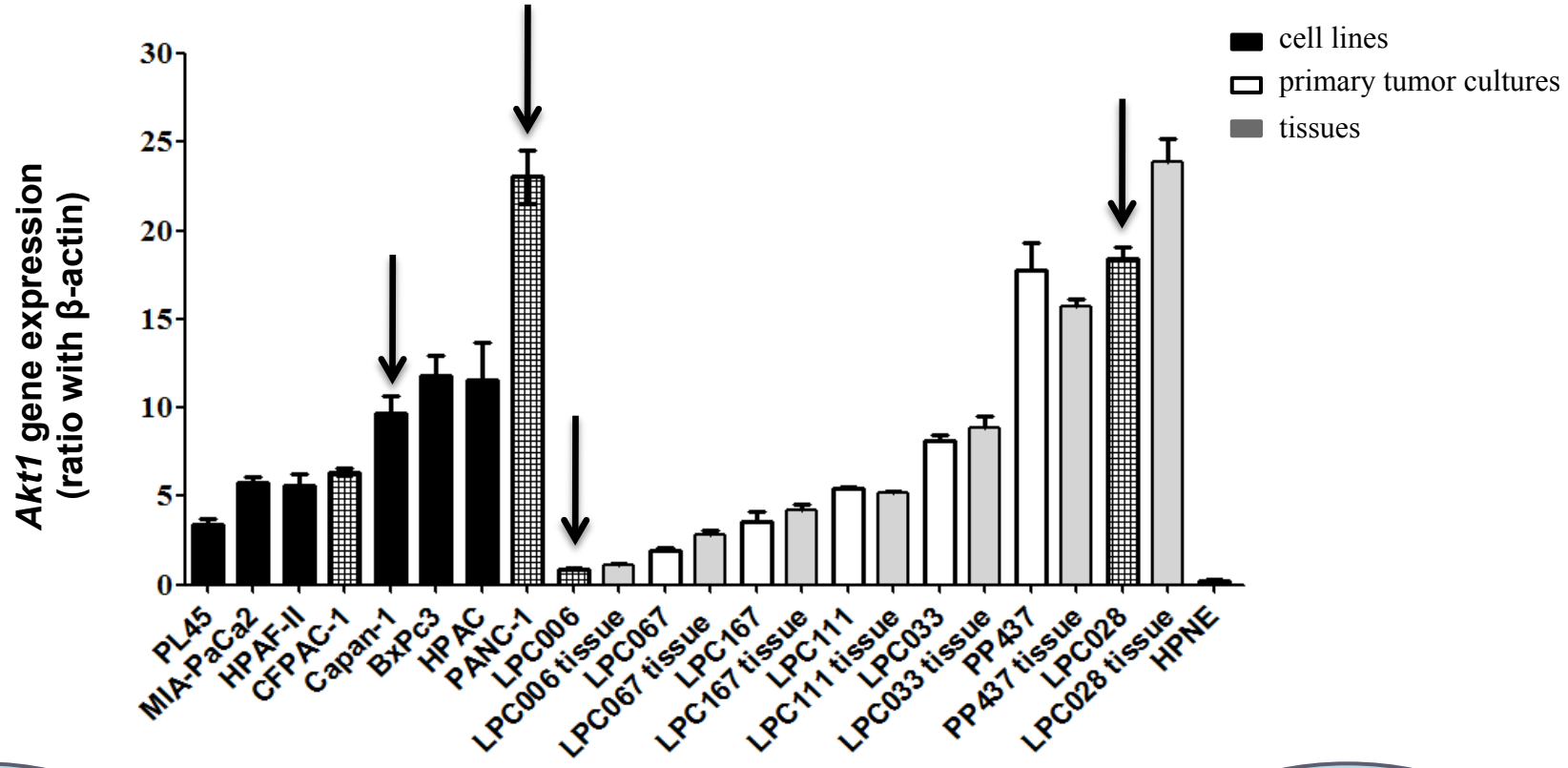








AKT1 mRNA expression



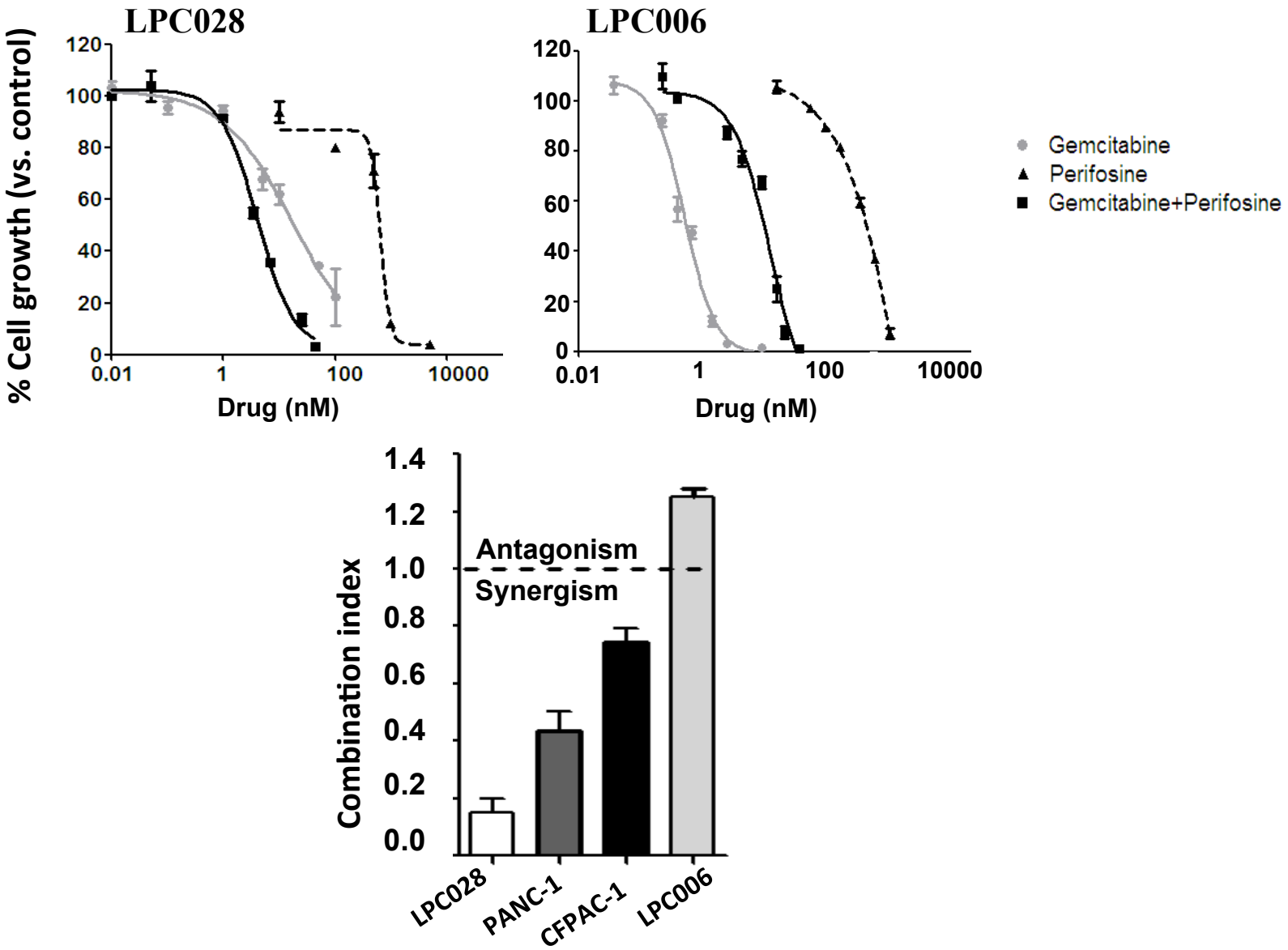
LPC028
High pAKT

LPC006
Low pAKT

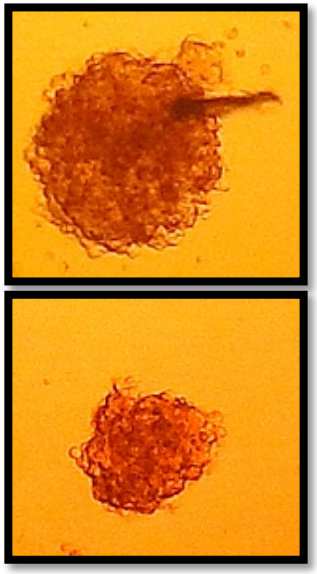
CFPAC
Low pAKT

PANC-1
High pAKT

PERIFOSINE INHIBITS CELL PROLIFERATION IN PDAC CELLS

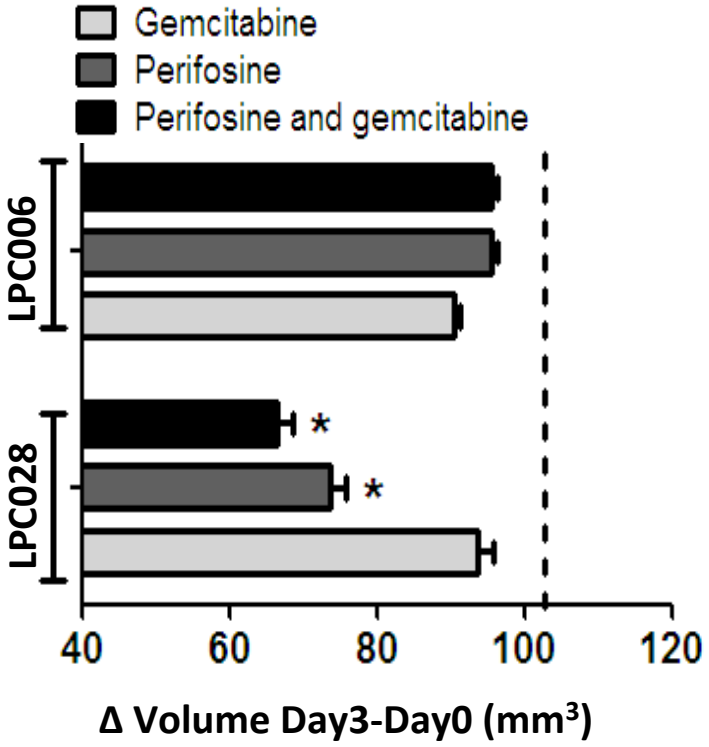


PERIFOSINE AND ITS COMBINATION WITH GEMCITABINE REDUCE THE SIZE OF PDAC **SPHEROIDS**

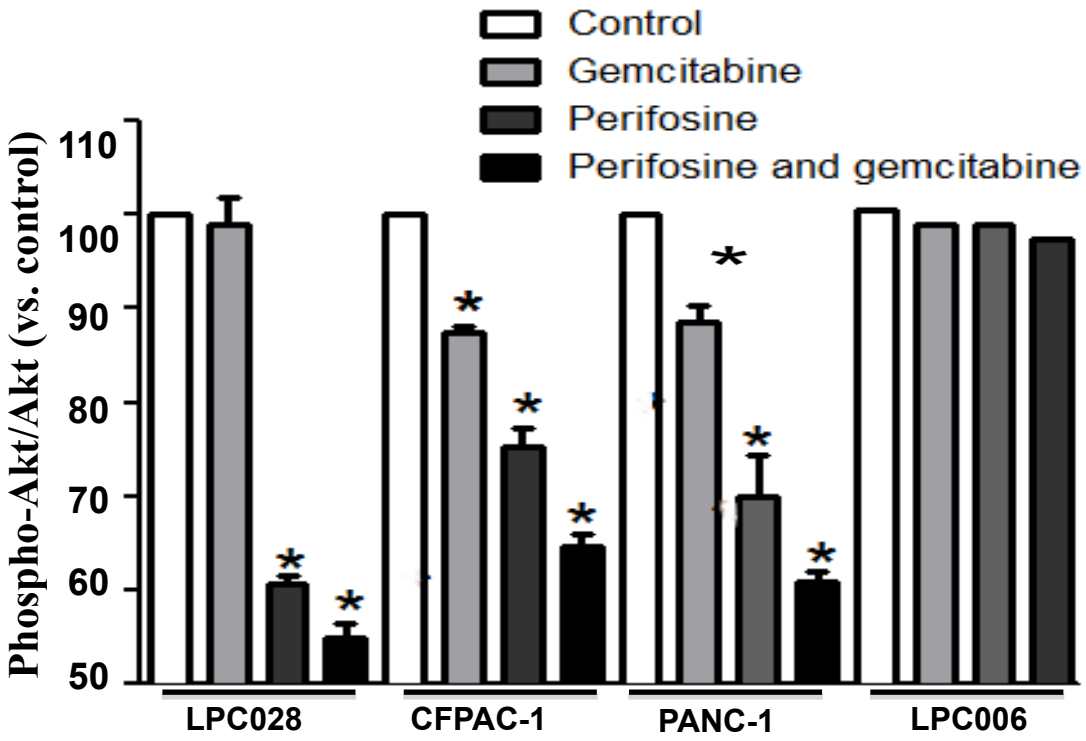


Control

Treated with Perifosine and gemcitabine

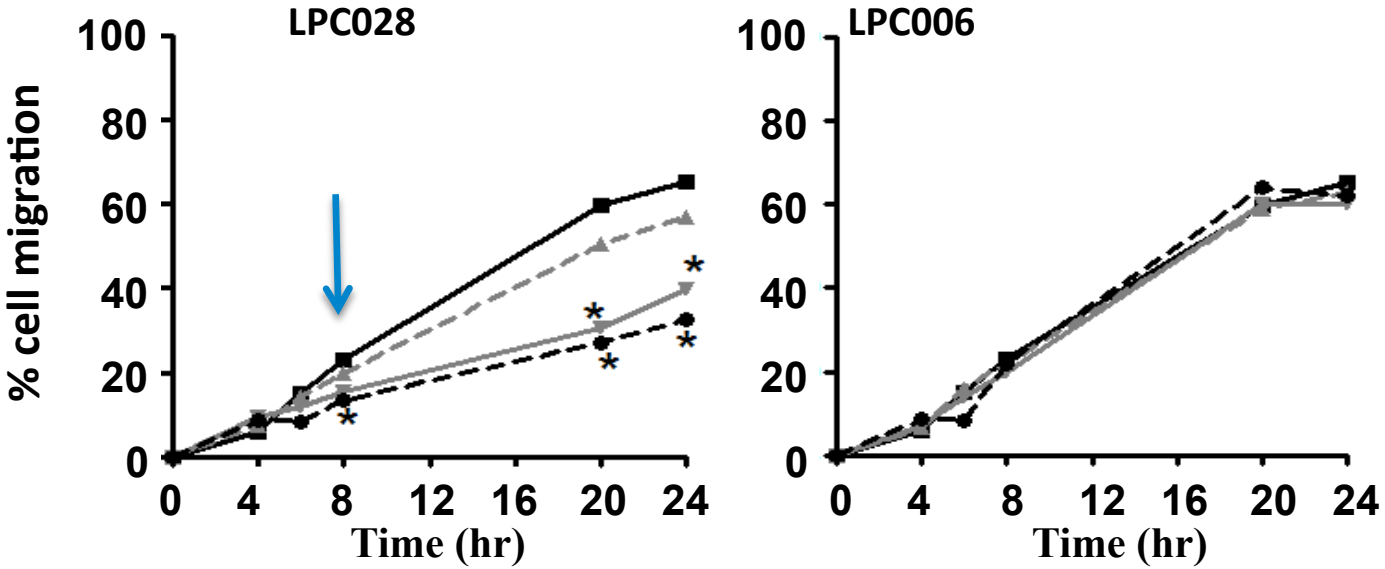


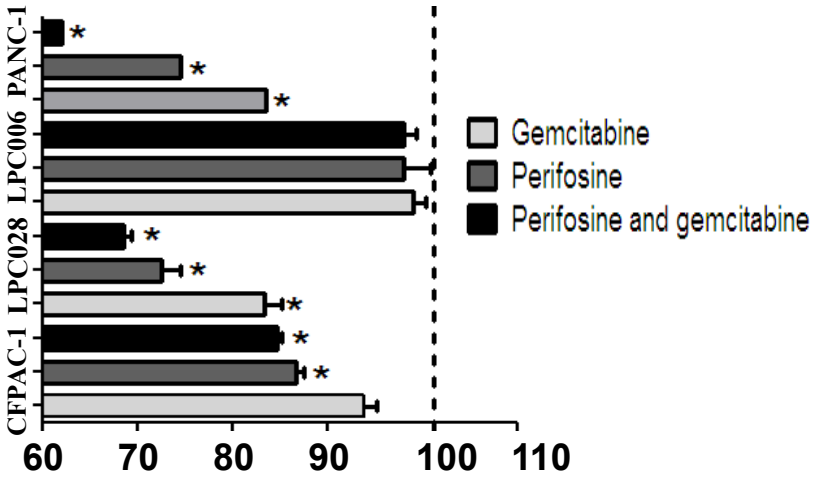
MODULATION OF PHOSPHO-AKT IN PDAC CELLS

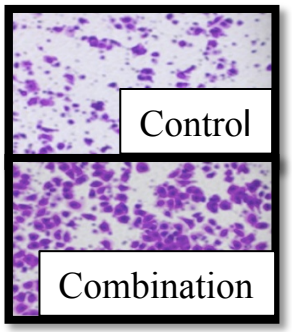


- Perifosine reduces the expression of p-Akt in LPC028, CFPAC-1 and PANC-1
- P-Akt levels in LPC006 are not affected

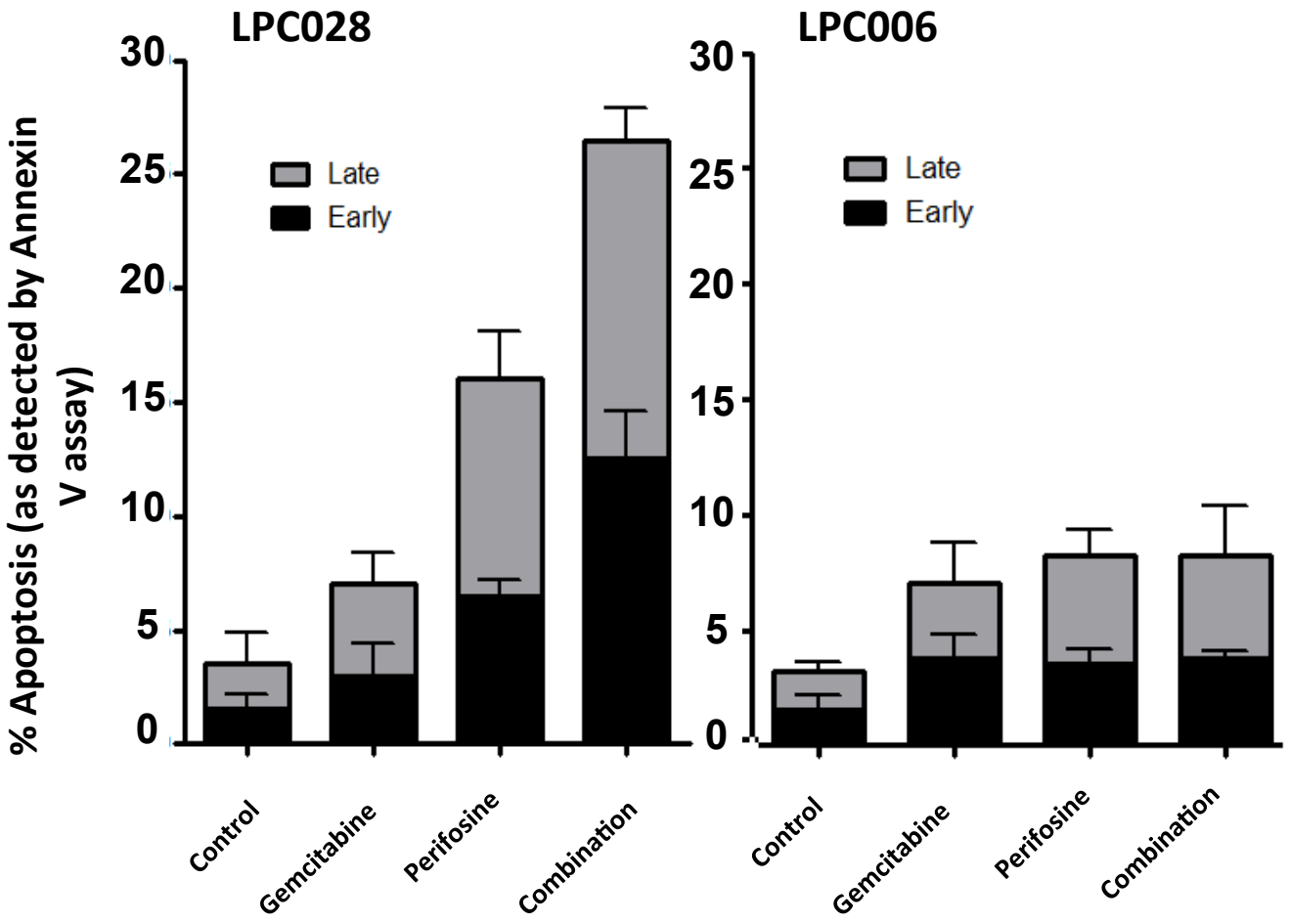
PERIFOSINE AND ITS COMBINATION WITH GEMCITABINE INHIBIT CELL **MIGRATION/INVASION**



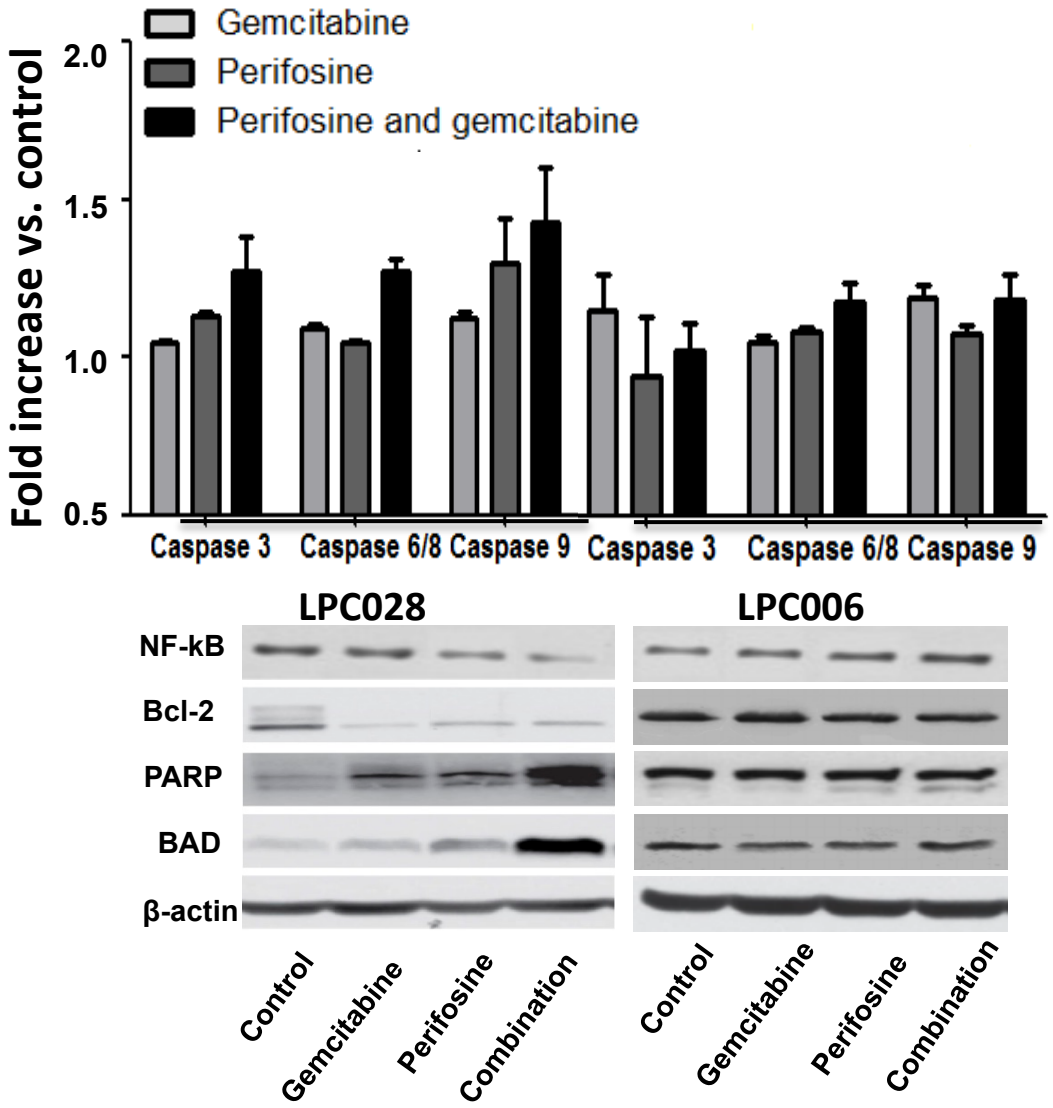


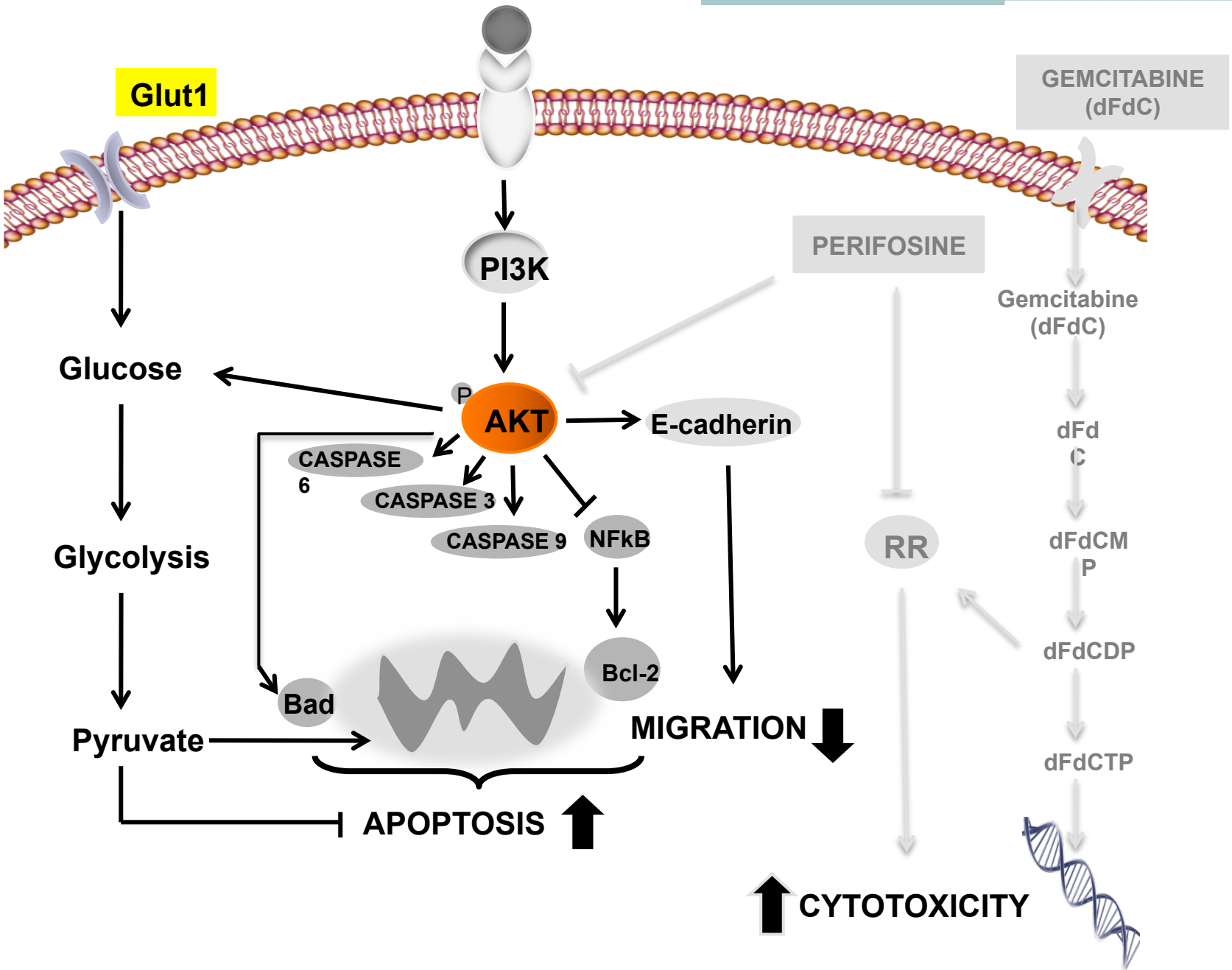


PERIFOSINE AND ITS COMBINATION WITH GEMCITABINE INDUCE **APOPTOSIS**



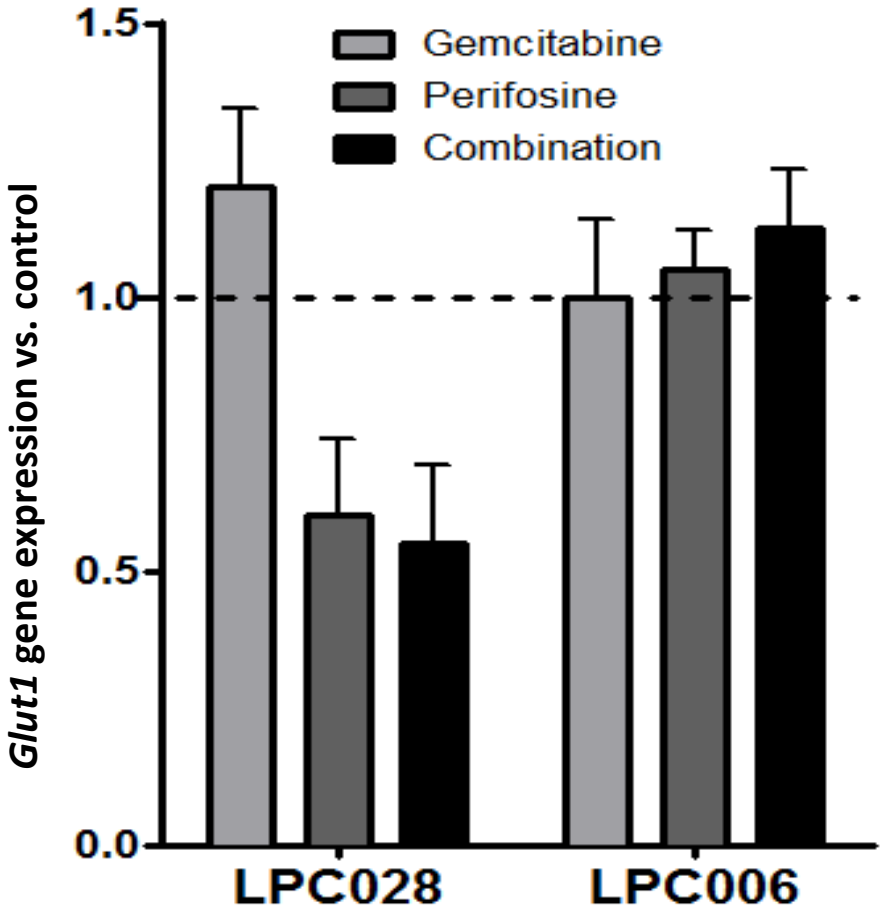
PERIFOSINE AND ITS COMBINATION WITH GEMCITABINE ACTIVATE **CASPASES** AND **PROAPOPTOTIC FACTORS**



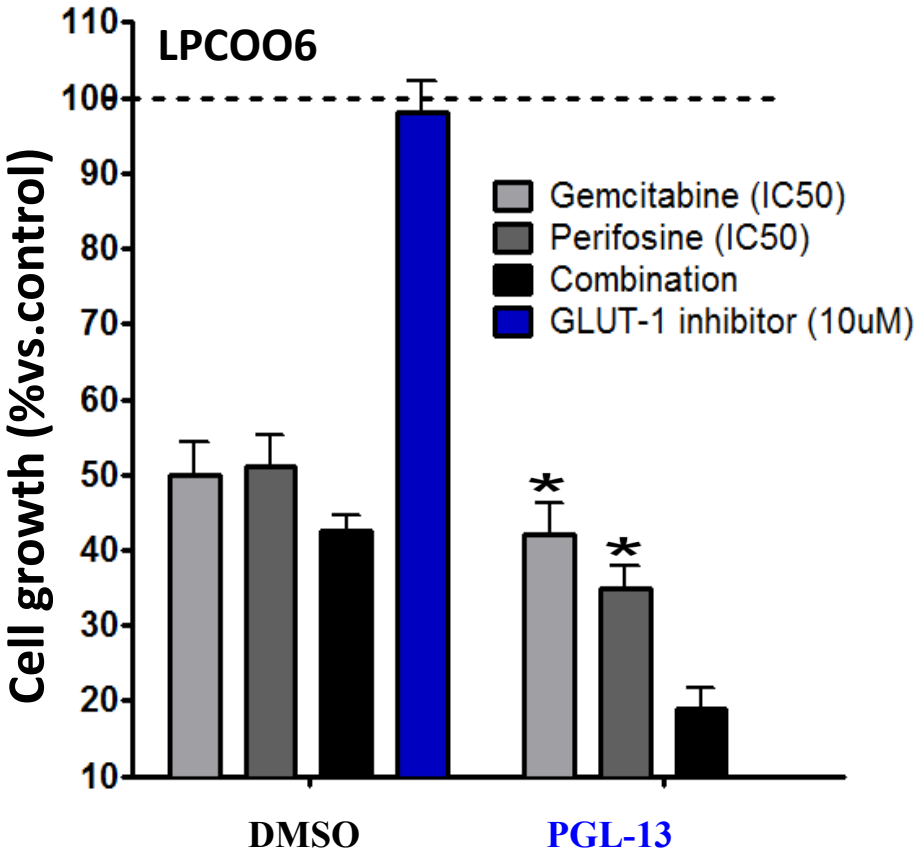

Glut1
GEMCITABINE (dFdC)
PI3K
PERIFOSINE
Gemcitabine (dFdC)
Glucose
P
AKT
E-cadherin
CASPASE 6
CASPASE 3
CASPASE 9
NFkB
dFd C
Glycolysis
RR
dFdCM P
dFdCDP
Bcl-2
Bad
Pyruvate
MIGRATION
dFdCTP
APOPTOSIS
CYTOTOXICITY

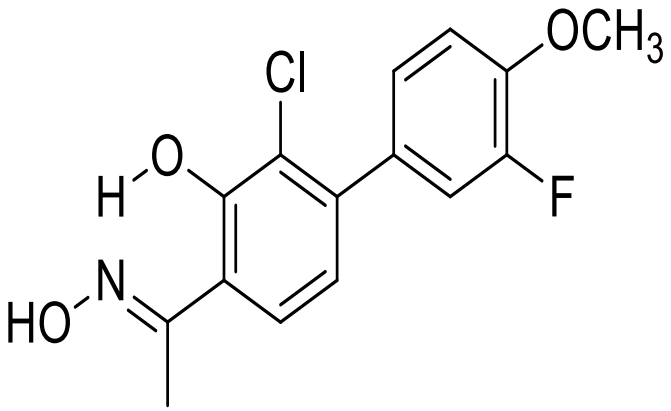
Glut1

Glut1 mRNA levels were significantly reduced after treatment with perifosine alone and in combination with gemcitabine in LPC0028



INHIBITION OF GLUT1 BY THE NOVEL SPECIFIC COMPOUND **PGL13**





CONCLUSIONS

- **Phospho-Akt expression emerges as both a prognostic biomarker**
- **Perifosine has a synergistic interaction with gemcitabine**
- **Phospho-Akt levels influence the antitumor activity of perifosine**
- **Inhibition of Glut1 overcomes resistance to this combination treatment**
- **Inhibition of Glut1 might represent a new therapeutic approach with Akt inhibitors in PDAC**