compared to the remaining isoforms. An increase in telomerase expression, AFP expression and secretion and cell proliferation reaching a maximum of two folds was observed after individual gene silencing of the four isoforms in HepG2/C3A cells; however, an inverse pattern was noticed when using PKC pan inhibitor Go6983. Similar results were observed in PLC cell line. The expression of the four isoforms increased in SNU-387 and SKOV-3 cells after 24 hour transfection. The effect persisted after 48 hour in SNU-387, contrary to SKOV-3 where the levels decreased returning to the controls expression levels.

Conclusion Taken together, decreased individual PKC isoforms rise telomerase expression and AFP secretion. However, PKC isoforms overexpression requires the presence of hTERT in AFP secretory cells. Thus, these results show for the first time the possible inter relation linking PKC isoforms to both AFP and hTERT in HCC.

PO-039 SOPHORIDINE INDUCES APOPTOSIS AND S PHASE ARREST VIA ROS-DEPENDENT JNK AND ERK ACTIVATION IN HUMAN PANCREATIC CANCER CELLS

[1]X Chen*, [1]Z Xu, [2]F Zhang, [1]C Zou, [1]Y Zhu, [3]H Zhong, [4]S Zhu. *[1]shanghai university of traditional Chinese medicine, School of Basic Medical Science, shanghai, China; [2]Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Department of General Surgery, shanghai, China; [3]Shanghai University of Traditional Chinese Medicine-, School of Basic Medical Science-, shanghai, China; [4]Shanghai University of Traditional Chinese Medicine, School of Basic Medical Science-, shanghai, China*

10.1136/esmoopen-2018-EACR25.84

Introduction Pancreatic cancer is generally acknowledged as the most common primary malignant tumour, and it is known to be resistant to conventional chemotherapy. Novel, selective antitumor agents are pressingly needed.

Material and methods CCK-8 and colony formation assay were used to investigate the cell growth. Flow cytometry analysis was used to evaluate the cell cycle and cell apoptosis. The peroxide-sensitive fluorescent probe DCFH-DA was used to measure the intracellular ROS levels. Western blot assay was used to detect the levels of cell cycle and apoptosis related proteins. Xenografts in nude mice were used to evaluate the effect of Sophoridine on pancreatic cancer cell *in vivo*.

Results and discussions Sophoridine killed cancer cells but had low cytotoxicity to normal cells. Pancreatic cancer cells were particularly sensitive. Sophoridine inhibited the proliferation of pancreatic cancer cells and induced cell cycle arrest at S phase and mitochondrial-related apoptosis. Moreover, Sophoridine induced a sustained activation of the phosphorylation of ERK and JNK. In addition, Sophoridine provoked the generation of reactive oxygen species (ROS) in pancreatic cancer cells. Finally, *in vivo*, Sophoridine suppressed tumour growth in mouse xenograft models.

Conclusion These findings suggest Sophoridine is promising to be a novel, potent and selective antitumor drug candidate for pancreatic cancer.

PO-040 CHARACTERISATION OF CDK12 KNOCKED OUT OVARIAN CANCER CELL LINES

R Chilà*, N Panini, F Guffanti, G Damia. *Institute of Pharmacological Research Mario Negri – IRCCS, Oncology, Milan, Italy*

10.1136/esmoopen-2018-EACR25.85

Introduction While cyclin-dependent kinases (CDKs) have a key role in promoting/controlling transition between the different phases of the cell cycle, transcriptional kinases, like CDK12, are mainly involved in gene transcription. CDK12 has been shown to regulate the expression of genes involved in DNA damage and to maintain genomic stability. Impairment of CDK12 activity is synergic with PARP inhibitor and cisplatin treatments in different cellular systems. We here aimed to generate ovarian cancer cell lines knocked out (KO) for CDK12 to understand its role in ovarian cancer and in response to chemotherapy.

Material and methods A2780 and SKOV3 CDK12 KO clones were generated with CRISPR/Cas9 technology. Cell cycle analysis was evaluated by standard flow cytometric methods and DNA repair genes levels by Real Time PCR. Caspase 3 activity was measured to detect apoptosis with a luminescence-based assay. Cytotoxicity experiments were performed treating cells with different drug concentrations and evaluating cell survival after 72 hours by MTS assay. For *in vivo* studies 7.5 millions of cells were transplanted subcutaneously in nude mice and animals were monitored for tumour appearance and growth.

Results and discussions We obtained 2 CDK12 KO ovarian cancer clones, A2780 KO and SKOV3 KO, out of more than 300 clones screened. The cell growth of both A2780 KO and SKOV3 KO cells is slower than the wild type (WT) cells, they have a less clonogenic ability and a tetraploid DNA content. Both CDK12 KO clones have a higher basal caspase activity than the WT cell lines, indicative of higher basal induction of apoptosis, while no increase in autophagy or senescence is observed. Both CDK12 KO clones show a decreased expression in BRCA1 and FANCD2 DNA repair genes than the WT cells. Cytotoxic experiments with anticancer agents with different mechanism of action show that both KO clones are less sensitive to ATM, CHK1 and WEE1 inhibitors treatment as compared to WT cells, while platinum and PARP inhibitors show similar cytotoxic activity in KO and WT cells. Interestingly enough, when KO clones were transplanted in nude mice, no tumour take was observed.

Conclusion We were able to obtain CDK12 KO cells. We think that these models could help in disclosing new roles of CDK12 in ovarian carcinoma and may represent a useful tool to study new combination therapies for tumours with CDK12 mutations.

PO-041 TNF PATHWAY IN METASTATIC COLORECTAL CANCER ACCORDING TO RAS STATUS AND IMPLICATION OF POTASSIUM CHANNELS

[1]S IBRAHIM*, [1]A Girault, [1]L Babin, [1]M Guéguinou, [2]M Potier-Cartereau, [2]C Vandier, [1]G Paintaud, [1]T Lecomte, [1]W Raoul. *[1]Tours University, GICC PATCH Team, Tours, France; [2]Tours University, Inserm U1069 N2C, Tours, France*

10.1136/esmoopen-2018-EACR25.86

Introduction Tumour necrosis factor α (TNF) is a key player in onco-inflammatory context but its implication in the progression of colorectal cancer (CRC) is still controversial. It is equally established that potassium channels contribute to tumour progression but their link to TNF-dependent microenvironment remains poorly described. Our aim is to investigate the effects of TNF on cellular models of colorectal cancer and