Material and methods In this perspective, the MCF-7 cell line was cultured for the examination of different molecular techniques including MTT, apoptosis analysis by ELISA, comet assay. Moreover, DNA ladder, AO/EB as another apoptotic cell analysis, markers of oxidative stress, and total antioxidant status, total thiol and GSH as non-enzymatic antioxidants assay were conducted.

Results and discussions The above techniques have proven that L1H is a better anticancer drug when compared to cisplatin as a positive control in human breast cancer cells, especially those affected by L1H. The findings clearly show that L1H evaluated in MCF-7 cell lines cause to rise or induced apoptosis, DNA damage, diminished antioxidant status against the increase of oxidised protein, and prevent cell proliferation.

Conclusion Manifold evidences supported our hypothesis that L1H has a potential therapeutically improved against the MCF-7 cell line, and then without doubt to be a suitable candidate drug for investigating cancers next.

PO-427 A NUCLEAR-DIRECTED HUMAN PANCREATIC RIBONUCLEASE VARIANT IS CYTOTOXIC FOR BREAST CANCER CELLS CULTURED IN 3D AND KILLS CANCER STEM CELLS

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Introduction Ribonucleases are a new class of antimurua RNA-degrading drugs that control the malignant phenotype at different levels. We produced nuclear-directed human pancreatic ribonucleases (ND-RNases) that showed selective cytotoxicity for tumour cells using two-dimensional cultures in vitro.

Material and methods Now we have studied the effect of the most effective ND-RNase in 2D cultures on different breast cancer cell lines representative of different molecular subtypes in three-dimensional assays.

Results and discussions The results show that the ND-RNase cytotoxicity is selective for these cancer cell lines grown in 3D in a laminin-rich extracellular matrix, a better model to predict drug sensitivity in vivo than cells cultured on a 2D substrate. On the other hand, we have studied the effect of this ND-RNase on the oncogenic cell signalling cascades through phospho-kinase array profiling assays. The results show that the ND-RNase strongly enhance phosphorylation of multiple signalling cascades in breast carcinoma cells. Moreover, we show that the ND-RNase have a marked ability to decrease the capacity of formation of mammospheres and their self-renewal in all breast cancer cell lines assayed.

Conclusion In conclusion, mammosphere formation assays are indicative that this ND-RNase is able to kill cancer stem cells, which are thought responsible for tumour progression, metastasis, resistance to therapy, and subsequent tumour recurrence. The pleitropic effects of this ND-RNase can be explained through its effect on the phosphorylation of multiple onco- genic cell signalling cascades.

PO-426 GENDER DISPARITY IN LUNG ADENOCARCINOMA SUSCEPTIBILITY IN EXPERIMENTAL MICE MODEL

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Introduction The endogenous causes of the gender differences observed in many cancers, however, many pharmacological mechanisms differences remain unclear. Our previous study demonstrated that sodium valproate (NaVP) has gender-related differences in urethane-induced lung tumorigenesis in the BALB/c mice model. Sodium dichloroacetate (DCA) is a pyruvate dehydrogenase kinase inhibitor, which has been suggested as a specific target in cancer. The aim of the study was to investigate possible treatment combination of DCA–NaVP on urethane-induced lung tumours in mice.

Material and methods BALB/c mice of both genders aged 4–6 weeks were investigated. Experiment consisted of the following groups: urethane-treated animals (n=13 female, n=11 male), urethane-treated and 6 months treated with 0.4% NaVP plus 0.05% DCA aqueous solution (every second week, beginning with NaVP) (n=17 female, n=15 male). These groups were compared with age and gender matched control groups (n=12). Urethane was given intraperitoneally with the total dose of 50 mg/mouse. After six months the animals were sacrificed. A standard hematoxylin-eosin staining was used.

Results and discussions All urethane-treated mice of both genders developed lung tumours. No lung tumours were found in control animals of both genders. The number of lung tumours per mouse did not differ in urethane-treated male (5.1±2.7) and female (5.5±2.6) mice groups. The incidence of adenocarcinoma was statistically significantly lower only in female DCA–NaVP treated group (0.82±1.1; p<0.003) as compared with the urethane-treated ones (2.0±0.71). No significant effects were found in male analogous groups.

Conclusion DCA–NaVP combination showed sex distinction affect in incidence of adenocarcinoma only in female mice group.

PO-428 THERAPEUTIC POTENTIAL OF NANOPARTICLE ENCAPSULATED WNT AND YAP INHIBITORS USING PATIENT DERIVED XENOGRAFT MODELS FOR THE TREATMENT OF TRIPLE NEGATIVE BREAST CANCER

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Introduction Triple negative breast cancer (TNBC) accounts for 15%–20% of all breast cancers but disproportionately accounts for the majority of breast cancer related deaths. Within TNBC, cancer stem cells (CSCs) exist in interconvertible mesenchymal or epithelial sub-populations that cannot be simultaneously targeted by non-specific chemotherapy highlighting the necessity of a therapeutic approach which targets both subpopulations.
However, these CSC populations differ dramatically, making therapeutic approaches illusive.

**Material and methods** Initially, we identified that Wnt and YAP signalling suppressed both mesenchymal and epithelial CSCs *in vitro* and *in vivo* using TNBC cell lines, patients’ tumour samples, and a database of 2509 patients with invasive breast cancer. Subsequently, we encapsulated Wnt and YAP inhibitors (PRI-724 and simvastatin respectively) in polyethylene glycol–polyactic acid nanoparticles (NPs) to increase intra-tumoral specificity and accumulation. Mice were implanted with patient derived xenografts (PDX) and were treated with NP-encapsulated PRI-724 and simvastatin. Additionally, NP accumulation within the tumour *versus* other organs was tracked using NP-conjugated fluorophores followed by flow cytometry and *in vivo* imaging system analysis (IVIS). To determine CSC and tumorigenesis, secondary transplantation was performed after NP treatment.

**Results and discussions** NP-encapsulated PRI-724 and simvastatin effectively suppressed Wnt and YAP gene expression *in vitro*. NP-encapsulated inhibitors were tolerable *in vivo* and accumulated in the TNBC PDX tumours. In contrast to paclitaxel (a commonly employed chemotherapeutic agent), NP-encapsulated PRI-724 and simvastatin markedly reduced the epithelial (ALDH⁺) and mesenchymal (CD44⁺/CD24⁻) CSC subpopulations. Additionally, co-administration of NP-encapsulated inhibitors with paclitaxel potently retarded the growth of TNBC PDX tumours but significantly maintained diminished epithelial (ALDH⁺) and mesenchymal (CD44⁺/CD24⁻) CSC populations.

**Conclusion** We developed a novel, tangible approach for the treatment of TNBC using NP-encapsulated Wnt and YAP inhibitors which accumulated in TNBC PDX tumours and potently retarded tumour growth, and inhibited CSC enrichment and tumorigenicity.