Material and methods In this perspective, the MCF-7 cell line was cultured for the examination of different molecular techniques including MITT, 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 rising 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-426 GENDER DISPARITY IN LUNG ADENOCARCINOMA SUSCEPTIBILITY IN EXPERIMENTAL MICE MODEL

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 intraaperitoneally with the total dose of 50 mg/mouse. After six months the animals were sacrificed. A standard hematoxylin–eosin staining was used. Lung tumours according to their morphology were divided into two groups: benign adenoma and adenocarcinoma.

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 (5.2±2.6) mice groups. The incidence of adenocarcinoma was statistically significantly lower only in female DCA–NaVP treated group (0.8±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.
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–poly(lactic 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 sources 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.

PO-429
ELASTIN-LIKE RECOMBINAMERS NANOPARTICLES: AN EFFECTIVE DRUG DELIVERY SYSTEM ON COLORECTAL CANCER CELLS
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Introduction With almost 1.4 million new cases each year worldwide, colorectal cancer kills 228,000 Europeans every year. Although new therapies have been discovered, the use of recombinant elastin-based biomaterials could open a new approach in cancer research as polymeric carriers for drug delivery in order to improve the accuracy of the action and reduce the toxicity of chemotherapeutic agents. In this work, we have developed a new elastin-like recombinamer (ELR) fused to a peptide inhibitor of the protein kinase Akt. This polymer self-assembled into nanoparticles, which showed killing ability on colorectal cancer cells (Caco-2).

Material and methods Taking advantage of the recombinant DNA technology, the constructs were formed by an amphiphilic backbone and several bioactive sequences, with an Akt inhibitor among others. ELR were produced by E. coli fermentation and, after purification process, were characterised and tested in vitro. Cellular viability assays on cancerous cells were carried out in order to study the killing ability of these nanoparticles.

Results and discussions Both physical and chemical characterisation of this novel ELR showed that it is able to self-assemble into nanoparticles with a diameter of 68 nm, which are an effective way to deliver the Akt inhibitor into the cytoplasm, where it will bind to its protein target Akt and stop the kinase activity. With a transition temperature of 18°C and a high negatively-charged surface, nanoparticles perfectly met all requirements for its use as biomedical tools. Moreover, nanoparticles showed increased killing ability on cancerous cells compared to non-cancerous cells.

Conclusion Thus, we have designed a new system able to enter into the cancerous cells and inhibit Akt signalling pathway. As an interesting advantage, ELRs have the ability to be modified by adding different molecules, such as aptamers or single chain antibodies, in order to be selectively targeted against cancerous cells. Thus, the action of these nanoparticles will be more accurate so as to achieve a new therapeutic tool for colorectal cancer treatment.

Poster Presentation: Experimental/Molecular Therapeutics, Pharmacogenomics

PO-431
ABSTRACT WITHDRAWN

PO-432
NEW COMBINED NANOPARTICLE THERAPY INHIBITS METASTATIC BREAST TUMOUR GROWTH WITH SUPERIOR EFFICACY AND LOWER SIDE EFFECT PROFILE TO DOCETAXEL
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Introduction Combining molecular therapies with chemotherapy may offer an improved clinical outcome for chemoresistant tumours. Sphingosine kinase 1 (SK1) is a proto-oncogene that is highly expressed in breast cancer, especially in oestrogen receptor (ER) negative tumours. SK1 inhibitor FTY720 has promising anticancer properties as monotherapy. In this study, we have developed and tested polymer and silicon nanoparticles combining docetaxel and FTY720 for enhanced anticancer effect, targeted tumour delivery and reduced systemic toxicity.

Material and methods Docetaxel, FTY720 and glucosamine were embedded or covalently conjugated to poly(lactic-co-glycolic acid) or silicon nanoparticles. Nanoparticles were characterised by dynamic light scattering and electron microscopy. The cellular uptake, cytotoxicity and in vivo antitumor efficacy of nanoparticles were evaluated.

Results and discussions Our data indicate that in ER negative breast cancer cells FTY720 provides chemosensitisation to docetaxel, allowing a four-fold reduction in the effective dose. We have encapsulated both drugs in nanoparticles, with narrow size distribution of ~100 nm and excellent cancer cell uptake providing sequential, sustained release of both drugs. In mouse models of human ER negative breast cancer nanoparticles had superior efficacy to systemic free docetaxel. Both polymer and silicon nanoparticles had significantly lower side effect profile including reduction of chemotherapy-induced weight loss, liver toxicity and neutropenia.