which correlates strongly with poor prognosis across a wide variety of cancers. We postulated that deletion of MPC may force ovarian cancer cells to use glutamine as a fuel source enabling their survival in glucose limited environments.

**Material and methods** Using ovarian cancer cell lines characterised as glutamine-addicted (SKOV3) or glutamine-independent (OVCA3) as exemplars, the impact of MPC1 on ovarian cancer cell metabolism was investigated by quantitative PCR, Western blotting, metabolic assays and the Seahorse XF Analyzer.

**Results and discussions** The importance of glutamine to an invasive phenotype is indicated by the observation that SKOV3 cells but not OVCA3 cells were migratory in the presence of glutamine. The functional significance of MPC as an important link between glycolysis and OXPHOS was shown by inhibiting MPC biochemically with UK5099. UK5099 altered glutamine-independent OVCA3 cells to emulate SKOV3 cells driving a switch to glutamine metabolism for OXPHOS. Whereas, non-inhibited OVCA3 cells, even in glucose free media, did not utilise glutamine for OXPHOS.

**Conclusion** The ability to model the switch from glutamine-independent to glutamine-addicted in ovarian cancer cells will allow us to investigate the metabolic and genetic changes that occur in progression from a low- to a highly-invasive cancer phenotype of ovarian cancer. This in turn will provide therapeutic targets to halt or slow ovarian tumour progression.

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**PO-258 TELMISARTAN INDUCES MELANOMA CELL APOPTOSIS VIA GENERATION OF ROS AND HAS SYNERGISTIC EFFECTS WITH TARGETED THERAPY IN VITRO**

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**Introduction** Melanoma is one of the most aggressive malignancies. A half of melanoma tumours carry BRAF V600E mutation, but despite dramatic initial effects of BRAF inhibitors in the clinic, patients eventually relapse, suggesting that combination therapies are needed to overcome resistance. BRAF inhibitors suppress glycolysis, yet the subsequent increase in oxidative stress due to the accelerated metabolism, which renders them more susceptible to oxidative-stress-induced cell death than the normal cells. In line with this notion, telmisartan-induced cell death could be ameliorated with N-acetyl cysteine. In addition, telmisartan synergized with both dacarbazine and vemurafenib in vitro and was still effective in A375R cell line, vemurafenib resistant cell line.

**Conclusion** Telmisartan has anti-melanoma potential in vitro and could increase the effectiveness of melanoma therapeutics, both conventional and BRAF inhibitor therapy. Our future efforts include elucidation of the exact mechanism by which telmisartan exerts these effects.

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**PO-259 INHIBITION OF THE HEXOSAMINE BIOSYNTHETIC PATHWAY BY TARGETING PGM3 CAUSES BREAST CANCER GROWTH ARREST AND APOPTOSIS**

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**Introduction** Cancer aberrant N- and O-linked protein glycosylation, frequently resulting from an augmented flux through the Hexosamine Biosynthetic Pathway (HBP), play different roles in tumour progression. Recent studies reported an association between the tumorigenic potential, metastasis and chemoresistance of several type of breast cancer cells and tumours, among which the Triple Negative Breast Cancer (TNBC), and the alteration of their membrane glycans composition and ramification as well as of their level of protein O-GlcNAc. However, the low specificity and toxicity of the existing HBP inhibitors prevented their use for cancer treatment.

**Material and methods** In order to identify a novel inhibitor of HBP pathway and in particular of the PG M3 enzyme, we performed a virtual screening by using computational approaches. These approaches lead us to the identification of a lead compound. This compound, named FR054, has been synthetized and in vitro and in vivo tested by using several biophysical methods (NMR, LC/MS, HPLC) and biochemical assay (CETSA, ITDRF, FACS analysis) as well as tested in TNBC xenograft mice model.

**Results and discussions** Here we report the preclinical evaluation of FR054, a novel inhibitor of the HBP enzyme PG M3, with a remarkable anti-breast cancer effect. In fact, FR054 induces in different breast cancer cells a dramatic decrease in cell proliferation and survival. In particular, in a model of Triple Negative Breast Cancer (TNBC) cells, MDA-MB-231, we show that these effects are correlated to FR054-dependent reduction of both N- and O-glycosylation level that cause also to a strong reduction of cancer cell adhesion and migration. Moreover we show that impaired survival of cancer cells upon FR054 treatment is associated with activation of the Unfolded Protein Response (UPR) and accumulation of intracellular ROS. Finally, we show that FR054 suppresses cancer growth in MDA-MB-231 xenograft mice.
Conclusion Our data support the advantage of targeting HBP for therapeutic purpose and encourage further investigation about the use of this small-molecule as promising compound for breast cancer therapy.

PO-260 ANTI-LYMPHOMA ACTIVITY OF NOVEL SELECTIVE GLUCOCORTICOID RECEPTOR AGONISTS (SEGRAS) IN VITRO AND IN VIVO

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Introduction Glucocorticoids (GCs) are widely used in blood cancer treatment; although, they cause metabolic disorders. Biological response to GCs is mediated by glucocorticoid receptor (GR) regulating gene expression via transactivation (TA), which requires GR binding to GC-responsive elements in gene promoters, and transrepression (TR), negative interaction between GR and transcription factors. TR mediates anticancer effects of GR, while side effects are associated with GR TA. Selective GR agonists (SEGRAs) that preferentially activate GR TR could be a better option for cancer treatment. One of well characterised SEGRAs is 2-(4-acetoxyphenyl)-2-chloro-N-methylethylammonium-chloride, or CpdA, isolated from Namibian shrub Salsola tuberculatiformis. CpdA demonstrated anticancer activity in vitro and in vivo. We extended SEGRA list by synthesis of CpdA enantiomers and its chemical derivatives.

Material and methods Synthesis of (S) and (R)-CpdA was based on Sharpless asymmetric dihydroxylation. Chemical analogues of CpdA, CpdA01-08, were designed by appending of bulky substituent into benzene ring and to nitrogen atom or alkylolation of carbon atom adjacent to chlorine atom. All experiments in vitro were carried out on Granta (lymphoma) and CEM (leukaemia) cells. Cells were treated with Dex, CpdA, (R) and (S)-CpdA, CpdA01-08. Effects on cell growth were evaluated by cell counting and flow cytometry. Affinity to GR was measured by competitive binding assay. Gene expression was measured by qPCR and Western blotting. GR and NF-kB activity was evaluated using Luciferase reporter analysis. Anticancer effect in vivo was determined using the model of murine lymphoma P388.

Results and discussions The most cytotoxic compounds among 10 newly synthesised, CpdA03 and CpdA05, demonstrated the highest affinity to GR. They induced GR TR but not TA and proved their SEGRA properties. Effect of CpdA enantiomers on cell growth and survival was not significantly different from Dex and CpdA. CpdA03, cytotoxic SEGRA with the highest affinity to GR, comparable with DEX and CpdA, was tested in vivo for evaluation its anti-lymphoma activity, and demonstrated 3-fold decrease of tumour size in comparison with 2-2.5-fold decrease after Dex or CpdA treatment.

Conclusion The design of synthesis and evaluation of anticancer properties of new SEGRA are provided. According to our data one novel SEGRA, CpdA03, is perspective for further investigation as anti-lymphoma drug with reduced side effects.

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