correlation was seen between response to COTI-2 or APR-246, suggesting that the compounds act differently in inhibiting cell growth.
Conclusion We conclude that targeting mutant p53 with COTI-2 is a potential new approach for treating p53-mutated TNBC.

PO-038 PDGFRβ AS A NEW BIOMARKER FOR METASTATIC TRIPLE-NEGATIVE BREAST CANCER: DEVELOPMENT OF A THERANOSTIC ANTI-PDGFRβ APTAMER FOR IMAGING AND SUPPRESSION OF METASTASES

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Introduction Triple-negative breast cancers (TNBCs) are a heterogeneous group of aggressive tumours lacking oestrogen and progesterone receptors and HER2 receptor, thus excluding the possibility of using targeted therapy against these proteins. Mesenchymal-like (ML) subtype, characterised by a stem-like, undifferentiated phenotype, is more invasive and metastatic than other TNBC subtypes and has a strong tendency to form vasculogenic mimicry (VM). Recently, platelet derived growth factor receptor β (PDGFRβ) has been shown to play a role in VM of TNBC. Regrettably, therapies targeting PDGFRβ with tyrosine kinase inhibitors are not effective in treating TNBCs, thus developing new strategies to target PDGFRβ in TNBC patients is crucial to improve their chances of survival. Here, we describe the characterisation of the Gint4.T anti-PDGFRβ nuclease-resistant RNA aptamer as high efficacious theranostic tool for imaging and suppression of ML TNBC metastases.
Material and methods Immunohistochemical analyses on a human TNBC tissue microarray was performed to correlate PDGFRβ expression with clinical and molecular features of different subtypes. Functional assays were conducted on PDGFRβ-positive ML BT-549 and MDA-MB-231 cells to investigate the effect of Gint4.T in interfering with cell growth in 3D conditions, migration, invasion and VM formation. Gint4.T was conjugated with near-infrared (NIR) fluorescent VivoTag-S680 and its binding specificity to receptor was confirmed both *in vitro* (confocal microscopy and flow cytometry analyses of TNBC cells) and *in vivo* (fluorescence molecular tomography in mice bearing TNBC xenografts). MDA-MB-231 cells were i.v. injected in nude mice and Gint4.T-NIR was used to detect lung metastases in mice untreated or i.v. injected with Gint4.T or a scrambled aptamer.
Results and discussions The expression of PDGFRβ was observed in human TNBC samples characterised by higher metastatic behaviour. Treatment of TNBC cell lines with Gint4.T aptamer blocked their invasive growth and vasculogenic properties in 3D culture conditions, and strongly reduced cell migration/invasion *in vitro* and metastases formation *in vivo*. The Gint4.T-NIR was able to specifically bind to TNBC xenografts and detect lung metastases *in vivo*. Therefore, the aptamer revealed a high efficacious theranostic tool for imaging and suppression of TNBC metastases.
Conclusion These studies indicate PDGFRβ as a new biomarker for ML and metastatic TNBC subtype and propose a novel targeting agent for the diagnosis and treatment of metastatic TNBCs.

PO-039 EXAMINATION OF THE ANTI-TUMOUR AND NEUROPATHIC SIDE EFFECT RESPONSES OF FIRST GENERATION AND SECOND GENERATION PROTEASOME INHIBITORS

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Introduction The overall goal in cancer treatment is to damage cancer cell macromolecules that causes the cancer cells to die. But in the treatment process, the defense mechanisms developed by the cancer cells affect the response to the treatment. As we have shown in our studies, cancer cells after anti-cancer stress have about 10–20 times more proteasome activation than healthy cells. Therefore, proteasome inhibition plays an important role in the prevention of resistance and recurrence in cancer treatment.

Bortezomib, the first generation proteasome inhibitor, is used intensively, in hematologic cancer types, and significantly increases patient survival. However, it causes significant side effects such as neuropathy. New proteasome inhibitors are being produced to reduce side effects in the market. These inhibitors include clinical studies as well as preclinical studies. However, the lack of side-effect studies causes the early termination of clinical trials.
Material and methods In this study, we compared the antitumour effects and neural toxicities of first generation and second-generation proteasome inhibitors in co-culture model. In this direction, human neural progenitor cells and K562 leukaemia cells were used. Co-cultures were incubated with 100 nM proteasome inhibitors for 24 hour and effects on the cancer cells and neural cells were analysed separately. Apoptotic cell death was evaluated with Annexin V/PI double staining by flow cytometry in K562 cells, and also PARP, Caspase 9 protein levels have been analysed in both cells. Protein oxidation related parameters such as protein carbonyls, ubiquitinated proteins, and HSP levels were investigated for understanding the stress response in both cells. Additionally, cytoskeleton proteins β-actin and β- tubulin changes were assessed in neural cells with confocal microscopy.
Results and discussions Our data showed that new proteasome inhibitors are less toxic in neural cells when compared to bortezomib. Protein carbonyls and ubiquitinated proteins were highest in bortezomib treated cells. On the other hand, especially carfilzomib has a lower anti-tumour activity in K562 cells when compared to bortezomib.
Conclusion This study may bring a highlight for the clinical usage and side effects of new proteasome inhibitors.

PO-040 DEVELOPMENT OF A TUNABLE FORM OF INTERFERON ALPHA FOR *IN VIVO* CANCER GENE THERAPY

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Introduction The immune system is a double-edge sword in cancer. On the one hand, it exerts immunosurveillance to eradicate

transformed cells that occasionally appear in the body; on the other hand, cancer cells can recruit immune cells endowed with pro-tumorigenic activity.

Our lab previously developed a strategy for targeted gene-based delivery of interferon alpha (IFNa) to tumours by tumour infiltrating monocytes/macrophages, which induces robust anti-cancer responses in several experimental models without inducing strong IFN responses in normal tissues as compared to systemic administration of recombinant IFNa. Whereas a sustained output could ensure long-term protection from tumour recurrence, it may raise concerns for long-term side effects, especially in case of cancer eradication.To overcome this issue, we are developing inducible strategies to control the amount of IFNa secreted in the tumour microenvironment.

Material and methods By fusing a destabilising domain (DD) to a protein of interest (POI) the former can confer its instability to the latter. This destabilisation can be rescued in a reversible and dose dependent manner with the addition of a small molecule specifically binding to the DD. To apply this technology to our strategy we have designed and *in vitro* tested different fusion proteins of IFNa (DD-IFNa). We also developed improved DD-IFNa with the addition of flexible and/or cleavable linkers and selected them for their capacity to be stabilised in a dose dependent manner in presence of their specific ligand *in vitro*.

Results and discussions Through this approach, we have identified effective fusion proteins with low basal activity and high fold induction upon ligand treatment. These novel tunable forms of IFNa are functional and their specific activity are comparable to the wild type cytokine in inducing IFN responsive genes.

Based on these promising *in vitro* results we are now translating these new platforms *in vivo* to test their efficacy in inducing anti-tumour responses in melanoma, colon and glioma models of cancer.

Conclusion In the perspective of clinical translation our approach can be used in the future to switch on/off the levels of IFNa in a tunable and personalised fashion for cancer eradication.

PO-041 COLD ATMOSPHERIC PLASMA: A POTENTIALLY SELECTIVE AND NON-INFLAMMATORY ANTI-CANCER THERAPY

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Introduction Considering the increased need for alternatives to current treatments, a new therapy based on plasma, the fourth state of matter, has recently raised the medical community's attention. The aim of this work was to evaluate the effect, selectivity and mechanisms of action of cold atmospheric plasma (CAP) in a human retinoblastoma cell line.

Material and methods An electronic device was designed to generate CAP, in open air above multiwell plates where Y79 cell cultures were seeded. Plasma emission spectrum was captured by a spectrometer. In order to evaluate the cytotoxicity and selectivity of CAP, metabolic activity of similarly treated Y79 and human fibroblasts HFF1 cells was measured. Apoptosis detection, analysis of mitochondrial membrane potential (MMP) and cell morphology were studied to determine the type of cell death. Propidium-iodide/RNAse staining was used to study the cell cycle and genotoxic effects were assessed by comet assay. Oxygen and nitrogen reactive species (RS) and oxidative defenses were measured. In order to explore the interaction of the electric field with voltage-gated calcium channels, blockade with verapamil was applied. Clonogenic assay screened for long term survival.

Results and discussions After 60 s of CAP treatment, the metabolic activity of Y79 cells decreased more than 50%, mostly due to apoptosis, while HFF1 endured viable. Cell survival was shortened. Accumulation of Y79 cells in S and G2/M phases was recorded, nevertheless, no DNA strand breaks were detected. Plasma emission spectrum displayed several peaks in ultraviolet domain. Concerning RS, the concentration of intracellular peroxides and nitric oxide was increased. However, antioxidative defenses were not triggered and reactive oxygen species inhibitors were not capable of abrogating cytotoxic effects of CAP. Similarly, verapamil did not protect cells from death.

Conclusion This study suggests a potential novel therapy based on plasma able to selectively target tumour cells while preserving the non-inflammatory environment.

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PO-042 TARGETING HYPOXIC PANCREATIC CANCER CELLS WITH GLUCOSE CONJUGATED LACTATE DEHYDROGENASE INHIBITOR NHI-GLC-2

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Introduction Pancreatic ductal adenocarcinoma (PDAC) is an abysmal disease with a 5 year survival rate of merely 8%. The tumour microenvironment is one of the factors contributing to PDAC chemoresistance. More specifically, the hypoxic tumour cores and the metabolic switch to aerobic glycolysis (e.g. the Warburg effect), contribute to the lack of drug response. Interestingly, two glycolysis components glucose transporter 1 (GLUT-1) and lactate dehydrogenase A (LDH-A) are overexpressed in PDAC. The latter, LDH-A, is also correlated with prognosis in metastatic PDAC.

N-Hydroxyindole-based LDH-A inhibitors (NHI-1 and NHI-2) have shown a synergistic effect in hypoxic PDAC cells when combined with gemcitabine. A glucose conjugated NHI-Glc-2 was designed to exploit the GLUT-1 overexpression in PDAC cells and in the present study we evaluated whether this novel compound further improved the pharmacological effect of LDH-A inhibitors.