formation assay suggesting that VM might be one mechanisms adopted by cells to avoid drugs exposure.

These findings suggest that acquisition of chemoresistance could cause a relapse of disease in which tumour cells take advantage of their capability to perform VM in order to self-sustain their growth and that may be cause of poor outcomes.

PO-473 QUANTIFICATION OF ERCC1-XPF COMPLEXES IN OVARIAN CANCER XENOGRAFTS WITH DIFFERENT SENSITIVITY TO CISPLATIN

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Introduction Epithelial ovarian cancer is the most lethal gynaecological cancer due to the development of resistance to a platinum based therapy. As DNA repair capacity is a key determinant for the cellular response to platinum (DDP) agents, DNA repair functional assays are required to study its relevance in DDP resistance. We set up a proximity ligation assay (PLA) to study the activity of nucleotide excision repair (NER) in patient derived ovarian carcinoma xenografts (PDXs) sensitive (S) and resistant (R) to DDP.

Material and methods Patient derived xenografts from fresh ovarian carcinomas were recently established in our laboratory. DDP antitumour activity was evaluated in most of the PDXs. Mice were sacrificed when tumours reached 1,5–2 gr. Tumours were fixed in formalin and paraffin embedded (FFPE). PLA was performed on tumour slides, using DuolinkII reagents (Sigma-Aldrich) and following the manufacturer instructions. PLA detects the presence of the protein complexes ERCC1-XPF, that are quantified as foci per nucleus and represent a biomarker of NER activity. Images were acquired by Olympus Virtual Slider (Olympus) and analysed with ImageJ software. Statistical analysis was performed with GraphPad Prism7.

Results and discussions Our xenobank comprises PDXs with different response to DDP: MNHOC266 and MNHOC230 are very sensitive to the drug, while MNHOC315 is resistant. We also obtained three sublines resistant to DDP (MNHOC124R, MNHOC124LPR and MNHOC239R) starting from sensitive PDXs (MNHOC124S, MNHOC124LPS and MNHOC239S), after several *in vivo* drug treatments. Statistically significant higher level of ERCC1-XPF foci could be observed in MNHOC124R and MNHOC124LPR as compared to their sensitive counterparts. No differences were observed between MNHOC239S and R PDXs, even if the number of ERCC1-XPF foci in MNHOC239S were statistically higher than the ones observed in MNHOC124S and in MNHOC124LPS. MNHOC266 and MNHOC230 showed levels of foci comparable to those of MNHOC124S and MNHOC124LPS. mRNA and protein levels of the different isoforms of ERCC1 and of XPF were not different among the PDXs studied.

Conclusion PLA for the detection of ERCC1-XPF complexes was set up in FFPE xenograft tumour slides. These preliminary results highlight a possible link between DDP resistance and higher NER activity that need to be confirmed in a wider panel of PDXs. In addition, these data confirm the importance to develop functional assays to directly evaluate the activity of different DNA repair pathways to predict DDP activity.

Poster Presentation: Experimental/Molecular Therapeutics, Pharmacogenomics

PO-475 UNRAVELLING THE ROLE OF SIALYLATION IN TARGETED THERAPY RESISTANCE USING 3D CANCER MODELS

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Introduction In the scenario of personalised medicine, targeted therapies are currently the focus of cancer drug development. These drugs can block the growth and spread of tumour cells by interfering with key molecules of malignancy. Receptor tyrosine kinases, major targets for treatment of advanced gastric cancer, are transmembrane glycoprotein receptors whose glycan modifications have been shown to modulate the receptor activation. In this work, we have addressed the role of aberrant glycosylation, specifically of sialylation, in gastric cancer malignancy and therapy resistance.

Material and methods To mimic the *in vivo* tumour features, an innovative 3D high-throughput cell culture methodology has been developed for gastric cancer cells. After in-depth characterisation of the gastric cancer spheroids, we evaluated the resistance of cell models glycoengineered for key sialylation-related enzymes by subjecting the spheroids to tyrosine kinase inhibitors that are currently in clinical use and preclinical trials.

Results and discussions The phenotypical and functional parameters assessed disclose that cell sialylation leads to different cellular adhesive and invasive features. Furthermore, we demonstrate that by applying 3D cell culture methods, the cell glycocalix undergoes changes compared to the conventional 2D culture systems. Remarkably, our glycomodels display strikingly different cell cytotoxicity response to several inhibitors of major oncogenic receptors. Furthermore, distinct activation levels of cell receptors are observed by applying targeted therapy drugs, altogether suggesting sialylation as an important mechanism of cancer drug resistance.

Conclusion Our results demonstrate that cell glycosylation, in addition to being a key feature of tumour progression, plays a critical role in therapy resistance to tyrosine kinase inhibitors in gastric cancer. These findings shed new light on the mechanisms underlying cancer drug resistance and propose aberrant sialylation as new predictive biomarker for patients' treatment response.

PO-476 INCREASED ERK PHOSPHORYLATION AS A CANDIDATE DRIVER OF RESISTANCE TO THE EXPERIMENTAL CANCER DRUG AT13148

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Introduction The AGC family of serine/threonine protein kinases comprises a number of drug targets with therapeutic potential