intratumoral 5 mg/kg or intraperitoneal 20 mg/kg injection) inhibited tumour growth in co-injection (PanC-1 + hPSCs) tumour model. Furthermore, we investigated whether AV3 could impair tumour growth in PDX pancreatic tumour model in mice. Intriguingly, co-treatment with AV3 (20 mg/kg, i.p., bis in 7 d.) and gemcitabine (50 mg/kg, i.p, bis in 7 d.) reduced the tumour growth by >80% compared to vehicle group. These effects were found to be due to the reduction of fibrosis in the tumour, as indicated by reduced αSMA and collagen I expression.

Conclusion This study shows AV3 is specific against ITGA5 which inhibits the activation of PSCs in vivo and inhibits pancreatic tumour growth in vivo.

PO-010 DUAL CHEMOTHERAPY AND PHOTODYNAMIC THERAPY: A SYNERGISTIC STRATEGY TO IMPROVE CANCER TREATMENT
1A Lazaro-Carrillo*, 2BM Simões, 2RB Clarke, 1,3A Villanueva. 1Universidad Autónoma de Madrid, Biology, Madrid, Spain; 2Manchester Cancer Research Centre- University of Manchester, Breast Biology, Manchester, UK; 3IMDEA Nanociencia, Nanomedicine, Madrid, Spain

Introduction Photodynamic therapy (PDT) is a clinical-approved option in several diseases characterised by uncontrollable cell proliferation, as cancer. PDT is recognised as a minimally invasive and toxic treatment. It is based on the administration of light activatable molecule known as photosensitizer (PS). After irradiation, a photochemical reaction between the PS and molecular oxygen leads to the generation of reactive oxygen species (ROS), which results in tumour regression.

Nowadays different strategies are being introduced in order to enhance PDT effectiveness, such as combination of PDT with chemotherapy or improvement of PS features.

Material and methods A new combined PDT-chemotherapy comprising two drugs widespread in clinical research – the hydrophobic Zinc(II)-phthalocyanine (ZnPc) as PS and the common chemotherapeutic agent doxorubicin (DOX) - was tested in tumour cell lines and primary cells obtained from patients affected by metastatic breast cancer. ZnPc was incorporated into nanoliposomes to increase its solubility and uptake into tumoral cells. This dual-therapy was also assayed in vivo (intravenously administrated) in a breast cancer xenograft model following tumour growth by luciferase activity.

Results and discussions MTT cytotoxicity assay showed that combination of both therapies remarkably increases the effectiveness of the treatment by inducing a synergistic cell death effect when compared to DOX or ZnPc monotherapy. In addition, annexin-V detection by flow cytometry, analysis of active caspase-3 and cytochrome c by immunofluorescence and time-lapse videomicroscopy corroborated a fine-tunable effect depending on light dose, leading to apoptotic or necrotic mechanism of cell death.

Subcellular location visualised by fluorescence microscopy confirmed internalisation of both drugs. Using DCFH-DA probe, we demonstrate that a significant higher ROS generation into cells was the main cause of the synergistic effect of this combined treatment. Further, mammmosphere formation efficiency assay (MFE) showed a reduced breast cancer stem cell activity in established cell line and primary cells obtained from patients, even using DOX at much lower concentration than clinical level. Finally, studies in human breast cancer xenografts indicated a high efficiency also in vivo.

Conclusion All these results provide novel and valuable information that contribute to consider chemophototherapy as a promising tool in current antitumoral treatments, potentially overcoming resistance to cancer chemotherapy and targeting cancer stem cells.

PO-011 DIHYDROARTEMISININ INHIBITS TCTP-DEPENDENT METASTASIS IN GALLBLADDER CANCER
F Zhang*, Shanghai Jiao Tong University Xinhua Hospital, Department of General Surgery, Shanghai, China

Introduction Patients with metastatic or relapsed gallbladder cancer generally have a poor prognosis. Therefore, targeting metastasis is one arm of therapeutic strategies to treat gallbladder cancer.

Material and methods Levels of translationally controlled tumour protein (TCTP) were measured in samples of gallbladder cancer by immunohistochemical staining. Wound healing, migration and invasion assays were used to investigate the motility of cells. Western blot assay was used to investigate the levels of TCTP and other proteins. Liver metastasis models and lung metastasis models were established to investigate the inhibitory effect of Dihydroartemisinin on gallbladder cancer metastasis.

Results and discussions TCTP is aberrantly expressed in gallbladder cancer patients and associated with metastasis and a poor prognosis. Depleting TCTP significantly inhibited gallbladder cancer cell migration and invasion. We found that Dihydroartemisinin as a potent inhibitor of TCTP inhibited TCTP-dependent cell migration and invasion by reducing cell division control protein 42 homolog (Cdc42) activation. In addition, in mice with xenografted tumours, treatment with Dihydroartemisinin decreased galbladder cancer cell metastases and improved survival.

Conclusion These findings provide new insights into the therapeutic activity of Dihydroartemisinin as a treatment for gallbladder cancer metastasis.

PO-012 PRE-CLINICAL INSIGHT INTO HOW PLATELET COUNT AFFECTS THE ACTIVITY OF HDACI RESMINOSTAT IN COMBINATION WITH THE MULTI-KINASE INHIBITOR SORAFENIB IN HCC
G Streubel*, S Schrepfer, U Parnitzke, R Krauss, M Borgmann, S Hamm. 4SC, Translational Pharmacology, Planegg-Martinsried, Germany

Introduction In a recent phase I/II clinical trial in hepatocellular carcinoma (HCC), (NCT02400788), the combination of HDAC-inhibitor resminostat (YH11001) with a multi-kinase inhibitor sorafenib was clinically beneficial compared to sorafenib monotherapy in patients with platelet counts \( \geq 1.5 \times 10^{11}/\mu l \), but not below that threshold. In HCC, platelets have been linked to bad prognosis, tumour growth and metastasis as well as to resistance against the standard treatment with sorafenib. This begs the question how platelets affect HCC cells and modulate their drug response.
Abstracts

Material and methods Several HCC cell lines were used to compare phenotypical features, susceptibility to platelets and drug-mediated effects. To determine effects on cancer cell features, in vitro cell growth and transwell invasion assays were performed. Furthermore, the underlying mechanism of a platelet-modulated drug response on the molecular level was explored.

Results and discussions In HCC cells, the anti-proliferative potency of sorafenib was counteracted by platelet factors and the mesenchymal phenotype. However, resminostat alone and in combination with sorafenib effectively triggered an anti-proliferative response independently of platelets or the mesenchymal phenotype. Therefore, resminostat determined the anti-proliferative response of the drug combination. Moreover, recent reports highlight HCC cell subpopulations which express cancer stem cell genes and harbour clonogenic growth and cell invasive capacities as critical for metastasis. Intriguingly, we found that platelets induced the cell-invasive capacity in HCC cells with detectable levels of several cancer stem cell markers and which featured a mixed epithelial-mesenchymal phenotype. Importantly, only the combination of resminostat with sorafenib, but not the mono-treatments, significantly reversed the platelet-induced cell invasion.

Conclusion Our pre-clinical data provide evidence on how platelets mediate pro-tumorigenic effects and modulate the therapeutic response to the resminostat/sorafenib drug combination. Platelet factors negatively modulated the drug response to sorafenib. This was overcome by the anti-proliferative activities of resminostat. Importantly, providing an explanation for the clinical benefit of the combination therapy, the platelet-induced invasive capacity was reversed only by the combination of resminostat with sorafenib, but not the mono-treatments.

PO-013 A NOVEL PEPTIDOMIMETIC TARGETING NRP1 INCREASES RADIOSENSITIVITY OF MEDULLOBLASTOMA STEM CELLS

C Gong*, 1A Almasoud, 1N Pellegrini-Moise, 1J Pinel, 1M Barbet-Heyob, 1P Chastagner, 1C Boura, 2Université de Lorraine- CNRS, Cran, Nancy, France; 2Université de Lorraine-CNRS, L2cm, Nancy, France; 3CHRU-Nancy, Pediatric oncology department, Nancy, France

Introduction Medulloblastoma (MB) is the most common paediatric malignant brain tumour. Recurrences occur in more than 40% of cases and sequelae are very important due to aggressiveness of the treatments. Cancer stem cells (CSCs) generate tumours through the stem cell patterns of self-renewal and differentiation into multiple tumour cell types and have better DNA repair capability inducing tumour resistance to radiotherapy (RT) and chemotherapy. Neuropilin-1 (NRP1) is involved in the progression of MB and seems to be in relation with the differentiation state of cancer cells. Recent molecular research has provided a better understanding of tumour development for the purpose of more targeted treatments. MR438 is a new sugar-based peptidomimetic targeting NRP-1. Our first results showed that MR438 seemed to induce the differentiation of MB stem cells. The objectives were therefore to demonstrate the effect of MR438 on in vitro and in vivo radiosensitivity.

Material and methods DAOY, D283Med and D341Med cell lines were used for obtaining cancer stem cells by in vitro enrichment. Clonogenic assays were performed on MB stem cells exposed to 0, 2, 4, 6, 10 Gy of RT in combination with MR438. For in vivo experiments, xenografted nude mice with 3 subgroup tumours were treated by RT at 2 Gy x 5 days in combination with MR438 and compared to Tuftsin in 6 groups (control, MR438, Tuftsin, RT, RT +MR438, RT +Tuftsin, n=6). Tumour volume was measured by calliper until a maximum of 45 days post-treatment, and then tumours were removed at the set end-points for clonogenic assay and cell viability.

Results and discussions Inhibition of NRP-1 via MR438 increased radiosensitivity of CSC models especially at the dose of 2 Gy. The DMF2 were 0.74, 0.89 and 0.88 for DAOY, D283-Med and Med-D341 cells respectively. In heterotopic models, a significant improvement of tumours radiosensitivity was also observed in the MR438 +RT group by comparing RT alone or MR438 alone (p<0.01). In an interesting way, the self-renewal capacity for CSCs after tumour dissociation was also decreased significantly when tumours were treated by MR438 +RT versus RT (p<0.05).

Conclusion This work showed the interest of targeting NRP-1 in association with radiotherapy to limit MB progression in decreasing the stem cells number in these tumours. Moreover, our in vivo experiments proved the possibility to use MR438 peptidomimetic as a radiosensitizing agent for treatment of MB.

PO-014 DIANHYDROGALACTITOL (VAL-083) REDUCES GLOBLASTOMA TUMOUR PROGRESSION IN VIVO, UPON BEVACIZUMAB-INDUCED HYPOXIA

A Golebiewska*, 1A Oudin, 2A Steino, 2JA Bacha, 2DM Brown, 1SP Niclou. 1Luxembourg Institute of Health, Norlux Neuro-Oncology laboratory- Department of Oncology, Luxembourg, Luxembourg; 2DelMar Pharmaceuticals, Preclinical Development, Vancouver, Canada

Introduction Standard-of-care for glioblastoma (GBM) includes surgery, radiation and temozolomide. Nearly all tumours recur and 5 year survival is less than 3%, largely due to chemoresistance. Unmethylated promoter status for O6-methylguanine-DNA-methyltransferase (MGMT) is a validated biomarker for temozolomide-resistance. Second-line anti-angiogenic treatment with bevacizumab has not improved survival and has been shown to induce intratumor hypoxia and increased chemoresistance. VAL-083 is a bi-functional DNA-targeting agent that readily crosses the blood-brain barrier. VAL-083 targets N7-guanine, causing DNA double-strand breaks and cancer cell-death in GBM cancer stem cells (CSCs) and non-CSCs, independent of MGMT. VAL-083 potency is increased in cancer cells with impaired homologous recombination (HR) DNA repair. Further, hypoxic cancer cells are known to downregulate their HR-pathway, proposing increased VAL-083 potency in hypoxic tumours. This suggests VAL-083 as part of a combination treatment with bevacizumab.

Material and methods Here, we assessed the response in vivo to VAL-083 +bevacizumab in an orthotopic GBM T16 PDX model to determine whether bevacizumab-induced hypoxia increased VAL-083 efficacy. All mice carried MGMT-unmethylated, temozolomide-resistant recurrent GBM T16 tumours detected by MRI 35 days post-implantation. Tumour progression was measured by MRI on days 49 and 56, and was calculated for the entire study (day 35 vs. 56) and for the last 7 days (day 49 vs. 56). VAL-083 treatment started 3 days after bevacizumab to ensure induction of hypoxia.