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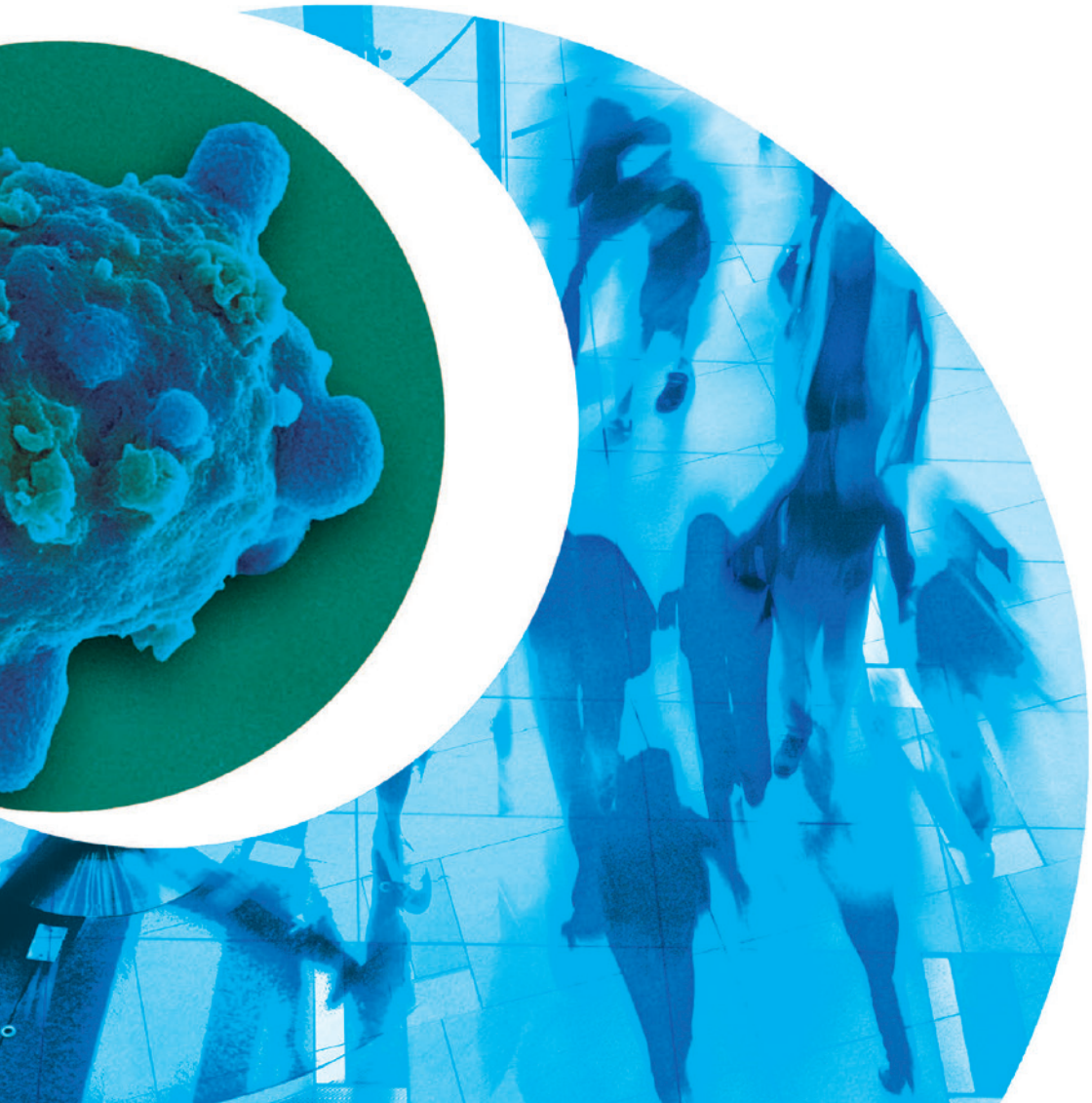
26–28 October 2022
Barcelona, Spain

ABSTRACT BOOK



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320 (PB100)

A Novel Hybrid Bifunctional Alkylating Agent That Potently Suppresses the Growth of mCRC Cells Xenografts and Patient-Derived Organoids

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Background: Hitherto metastatic colorectal cancer (mCRC) is the basis for the second-leading death of all cancers. As the first-line chemotherapy in mCRC treatment, an antiangiogenic combination of bevacizumab with FOLFOX4 improved the competence and overall survival (OS). We developed a new hybrid small molecule with dual properties as first-line therapy to study its synergistic effect on CRC cell lines and patient-derived organoids.

Materials and methods: The anti-proliferative effect was analyzed by PrestoBlue assay using CRC cell lines and CRC patient-derived organoids (PDO). Antiangiogenic property has been assessed using the docking model, molecular, *in vitro*, and *in vivo* methods. Xenografts of CRC cell lines and PDOs were tested for BO-2762 efficacy with 20 mg/kg (*i.v*) using nude mice. For safety profiling and toxicology, the ICR mice model has been used for various pathological analyses.

Results: We identified ant proliferative IC_{50} ranged between 0.5 to 4.5 μM against CRC cell lines and PDO cell lines. Subsequently, DNA damage has been observed by inter-strand cross-linking (ICL) in alkaline agarose gel and cell lines. ICL affects the cellular DNA synthesis by arresting the cell cycle at S Phase upon apoptosis. Angiogenesis inhibition occurred by inhibiting VEGFR2 activation on endothelial cells with anti-proliferative IC_{50} of 3 μM and in the mouse as well. Based on in vitro analysis, metastatic and non-metastatic cells (LoVo, SW620, LS1034, and HT-29) and PDOs (T_{53} and T_{112}) induced xenografts have shown effective growth inhibition with 85.8%, 83.0%, 75.4%, and 44.8% respectively. PDO xenografts have shown a tremendous inhibition of more than 90% of growth reduction. Pathological analysis elaborates the effect of BO-2762 treatment by elevating γ-H2AX and CD31 expression in treated mice tumor tissues. Biosafety analysis has shown promising safety parameters in blood chemistry and pathology analysis.

Conclusions: BO-2762 is a potent anti-cancer agent to mCRC. The mice model indicates that BO-2762 driven bifunctional properties induced serious DNA damage and inhibited angiogenesis leading to promising inhibition of tumor growth as first-line chemotherapy properties with a satisfying safety profile.

No conflict of interest.

321 (PB101)

High content screening of ovarian organoid models to accelerate anti-cancer drug discovery

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Background: Establishment of advanced *in vitro* ovarian cancer organoid models provides a rapid and biologically relevant platform for testing novel cancer (immune) therapies. These ovarian models, when cultured alone or in co-culture with other cell types, serve as a great tool for predicting treatment responses in patients, discriminating different drug responses, and flagging off-target effects. In this study a high throughput platform that combines 3D cultured ovarian models with phenotype-based image analysis is presented. This platform allows the measurement of clinically relevant endpoints beyond conventional cell viability, including those associated with tumor killing, growth inhibition, toxicity, different types of cell death and interactions with added immune cells.

Methods: A panel of genetically characterized ovarian cancer organoid models was cultured in a natural extracellular matrix scaffold to mimic *in vivo* complex biology. To investigate the effects of standard-of-care (SoC) treatments, a library of small molecules and novel targeting antibodies on tumor outgrowth, the following organoid test systems were set up: 1. Compound profiling on various ovarian cancer organoids alone or in combination with irradiation; 2. High throughput compound library screen in a panel of ovarian models; 3. Co-culture of ovarian cancer organoids with PBMCs and cancer associated fibroblasts (CAFs).

Results: High content 3D image analysis of ovarian organoids upon various treatments enables sensitive detection of treatment-induced and compound-specific morphological changes such as (inhibition of) growth, development, lumen formation, epithelial integrity and cell death or discrimination of cellular interactions in a complex tumor co-culture microenvironment. Ovarian organoids with specific mutations and diverse genetic backgrounds show various sensitivity to the treatments alone or in combination with irradiation or relevant immune cells.

Conclusions: Our high content image analysis of *in vitro* 3D cultured organoids represents a rapid, reproducible and physiologically relevant model system for testing various candidate compounds (e.g., antibodies, antibody-drug conjugates, small molecules, oncolytic viruses or immuno-therapies) that target, for example, ovarian cancer. This platform is suitable for high throughput screening in a panel of organoids but also for in-depth mode of action study in mono- or co-culture systems. Therefore, our ovarian organoid screening platform represents a significant advance on conventional *in vitro* models and helps bridge the translational gap between *in vivo* and conventional *in vitro* studies.

No conflict of interest.

322 (PB102)

Cationic amphiphilic drugs as potential anticancer therapy for PDAC

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) is the sixth leading cause of death worldwide. PDAC carries a 5-y survival of less than 10%, as it is often diagnosed at a late stage and is widely refractory to available therapies. PDAC tumors are hypoperfused, resulting in poor nutrient delivery. To exist in this hostile microenvironment, PDAC cells rely on intracellular and extracellular scavenging pathways to acquire metabolic substrates for growth. Autophagy and other lysosome-dependent recycling pathways are aberrantly regulated in PDAC. Although autophagy modulation is an emerging therapeutic strategy for PDAC, the co-dependences induced by lysosomal inhibition have not been systematically explored. Cationic amphiphilic drugs (CADs) accumulate in lysosomes, destabilize their membranes, and can have anti-tumorigenic effects. CADs include hundreds of pharmacologic agents used to treat a broad spectrum of common diseases. The aim of this study was to investigate anti-PDAC activity of several clinically-approved and newly synthesized CADs.

Material and methods: Imidazoline, quinoline, and chrysene derivatives were examined. Anti-tumor activity of CADs was evaluated in human PDAC cell lines *in vitro* and in Tg(fli1:EGFP) zebrafish model *in vivo*. Effects on mitochondria, lysosomes, and autophagy flux were examined by immuno-fluorescent microscopy. Levels of reactive oxygen species (ROS), changes in the mitochondrial membrane potential, and induction of apoptosis by the selected CADs were evaluated by flow cytometry.

Results: The newly synthesized derivatives of quinoline and chrysene induced apoptosis in PDAC cells *in vitro* in the 2–10μM range, while the only FDA-approved imidazoline with apoptotic activity was rilmenidine, at doses higher than 100μM. Most of the tested compounds induced the expansion of the acidic compartment, as measured by acridine orange and LAMP1 staining, and modulated autophagy, as seen by LC3 staining intensity and distribution. Mitochondrial oxidative stress was induced by the tested CADs as well as the dissipation of the mitochondrial membrane potential ($\Delta\Psi m$). Ultimately, both newly synthesized CADs and rilmenidine limited the growth and spread of PANC1 cancer cells in the Tg(fli1:EGFP) zebrafish model.

Conclusion: Quinoline and chrysene CADs had the potential for a dual lysosome/mitochondrion targeting in PDAC cells and were inducing apoptosis almost in a nM range. While rilmenidine was less potent than newly synthetized CADs in inducing cell death *in vitro*, all the tested compounds had significant anti-tumor effects in the zebrafish model. These results imply that CADs have promising anti-PDAC effects and that effects on the other cells in the tumor microenvironment other than the cancer cells themselves have to be examined.

No conflict of interest.