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

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Background: Histologically 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 an antiproliferative IC50 range 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 IC50 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 (T24 and T1) 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 γH2AX and C/EBPb expression in treated mouse tumors. 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 in vivo, BO-2762 driven biological properties indicate a 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.

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 (immuno) 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: Using 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 mutation and clinical 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 ovarian organoids represents a rapid and 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.