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PO-423 NOVEL 4,5,6,7-TETRAHYDROPYRAZOLO[1,5-A]PYRIDINE FUSED CHLORINS AS VERY ACTIVE PHOTOSENSITIZERS AGAINST MELANOMA AND BLADDER CANCER CELLS

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Introduction Photodynamic therapy (PDT) is a clinically approved therapeutic procedure, which is entering the mainstream of cancer treatments. Nowadays PDT has been successfully used in the treatment of skin cancers, but the use of PDT against melanoma can be compromised due to the natural resistance mechanism of some melanoma cancer cells. Thus, the search for new photosensitizers is a relevant research goal. Bladder cancer is also an interesting target to PDT, due to easy irradiation accessibility by cystoscopy.

Material and methods A375 human melanoma cells and HT1376 human bladder cancer cells were plated. The formulation of the sensitizers consisted in a 1 mg/mL solution in DMSO and the desired concentrations being achieved by successive dilutions. The sensitizers were administered in several concentrations (from 1 nM to 10 mM) and cells were incubated for 24 hour. Controls were performed on every test. Cells were washed with PBS and new drug-free medium was added. Each plate was irradiated with a fluence rate of 7.5 mW/cm², to reach 10 J. Evaluation by MTT assay was performed 24 hour after the photodynamic treatment in order to evaluate the cytotoxic effect.

Results and discussions Our previous in vitro PDT studies demonstrated that the increase of chlorins’ hydrophilicity of leads to higher activity against A375 melanoma cells. Therefore, a series of novel 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-fused chlorins bearing dicarboxylic acid and monocarboxylic moieties were developed showing an interesting biological activity against the A375 and HT1376 cancer cells. Inhibition of the metabolic activity seems to be dependent on the concentration of the sensitizers used. With the experimental metabolic activity values, it was possible to calculate the concentration of the sensitizers that inhibits the proliferation of cultures in 50% (IC50). For this series of compounds, IC50 values ranged from mM to nM concentrations. Nevertheless, a new molecule with an IC50 value of 67.93 nM stood out.

Conclusion The compounds tested were active against human melanocytic melanoma A375 cells and human bladder HT1376 cancer cells. MTT assay showed that the metabolic activity was inversely proportional to the concentration of the photosensitizer. Interestingly low IC50 values in the nanomolar range encourage further studies.

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PO-424 DISCOVERY OF A NOVEL SMALL MOLECULE STING AGONIST AS A NEW CANCER IMMUNOTHERAPY

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Introduction Harnessing CD8 T cells to respond to tumorigenic antigens remains a supreme therapeutic strategy for sustained clearance of tumours and a resulting cancer-free life for patients. Efficient tumor-initiated T cell priming requires interferon-beta (IFN-b) production by dendritic cells and the expression of IFN-b has been demonstrated to be dependent upon activation of the Stimulator of Interferon Genes (STING) pathway. Indeed, intratumoral delivery of nucleotide-based STING agonists induces a profound regression of established tumours in syngeneic mouse models.

Material and methods Here, we describe a high-throughput screening platform for identifying non-nucleotide small molecule STING agonists. This has been established using a primary assay involving a human THP-1 cell line carrying an IRF-inducible reporter with 5 copies of the IFN signalling response element. Counter screens, involving alternative reporter constructs, rodent cell-based assays, as well as cGAS and STING knockout cell lines, are used to eliminate luciferase artefacts and ensure human-rodent cross species reactivity, as well as pathway selectivity. Biochemical assays, involving cGAS enzymatic activity and STING protein binding assays, are used to identify the specific target of identified hits.

Results and discussions To date, from an initial screen of ~1 000 000 compounds we have identified at least one novel highly tractable STING agonist scaffold (SRCB-0001, EC50 ~10000, –1 μM), which induces expression of a type I interferon-stimulated gene signature in relevant cell types and IFN-b protein production in human peripheral blood mononuclear cells (PBMCs) with efficacy that is comparable to that observed for 2‘,3‘-cGAMP, a natural dinucleotide STING ligand. Unlike nucleotide-based STING agonists, we have found that SRCB-0001 can be dosed orally in mice thereby lifting the restrictions of intratumoral injection as the route of administration.

Conclusion Thus, we propose SRCB-0074 as a first-in-class small molecule STING agonist for immuno-oncology applications.

PO-425 THE EFFECT OF BIS STRUCTURED SCHIFF BASE MATERIAL ON APOPTOSIS, CYTOTOXICITY AND DNA DAMAGE OF BREAST CANCER CELL LINE

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Introduction Developing new anti-cancer agents are crucial for cancer treatment. Antiproliferative activity of L1H as bis structured schiff base was subjected to preliminary research in eight different kinds of cell lines by cell viability method using different concentrations of it to determine their inhibitory concentration. L1H demonstrated the highest cytotoxicity in human breast cancer cell line MCF-7.
Introduction

The endogenous causes of the gender differences observed in many cancers, however, many pharmacological mechanisms differences remain unclear. Our previous study demonstrated that sodium valproate (NaVP) has gender-related differences in urethane-induced lung tumorigenesis in the BALB/c mice model. Sodium dichloroacetate (DCA) is a pyruvate dehydrogenase kinase inhibitor, which has been suggested as a specific target in cancer. The aim of the study was to investigate possible treatment combination of DCA–NaVP on urethane-induced lung tumours in mice.

Material and methods

BALB/c mice of both genders aged 4–6 weeks were investigated. Experiment consisted of the following groups: urethane-treated animals (n=13 female, n=11 male), urethane-treated and 6 months treated with 0.4% NaVP plus 0.05% DCA aqueous solution (every second week, beginning with NaVP) (n=17 female, n=15 male). These groups were compared with age and gender matched control groups (n=12). Urethane was given intraperitoneally with the total dose of 50 mg/mouse. After six months the animals were sacrificed. A standard hematoxylin–eosin staining was used. Lung tumours according to their morphology were divided into two groups: benign adenoma and adenocarcinoma.

Results and discussions

All urethane-treated mice of both genders developed lung tumours. No lung tumours were found in control animals of both genders. The number of lung tumours per mouse did not differ in urethane-treated male (5.1±2.7) and female (5.5±2.6) mice groups. The incidence of adenocarcinoma was statistically significantly lower only in female DCA–NaVP treated group (0.82±1.1; p<0.003) as compared with the urethane-treated ones (2.0±0.71). No significant effects were found in male analogous groups.

Conclusion

DCA–NaVP combination showed sex distinction affect in incidence of adenocarcinoma only in female mice group.