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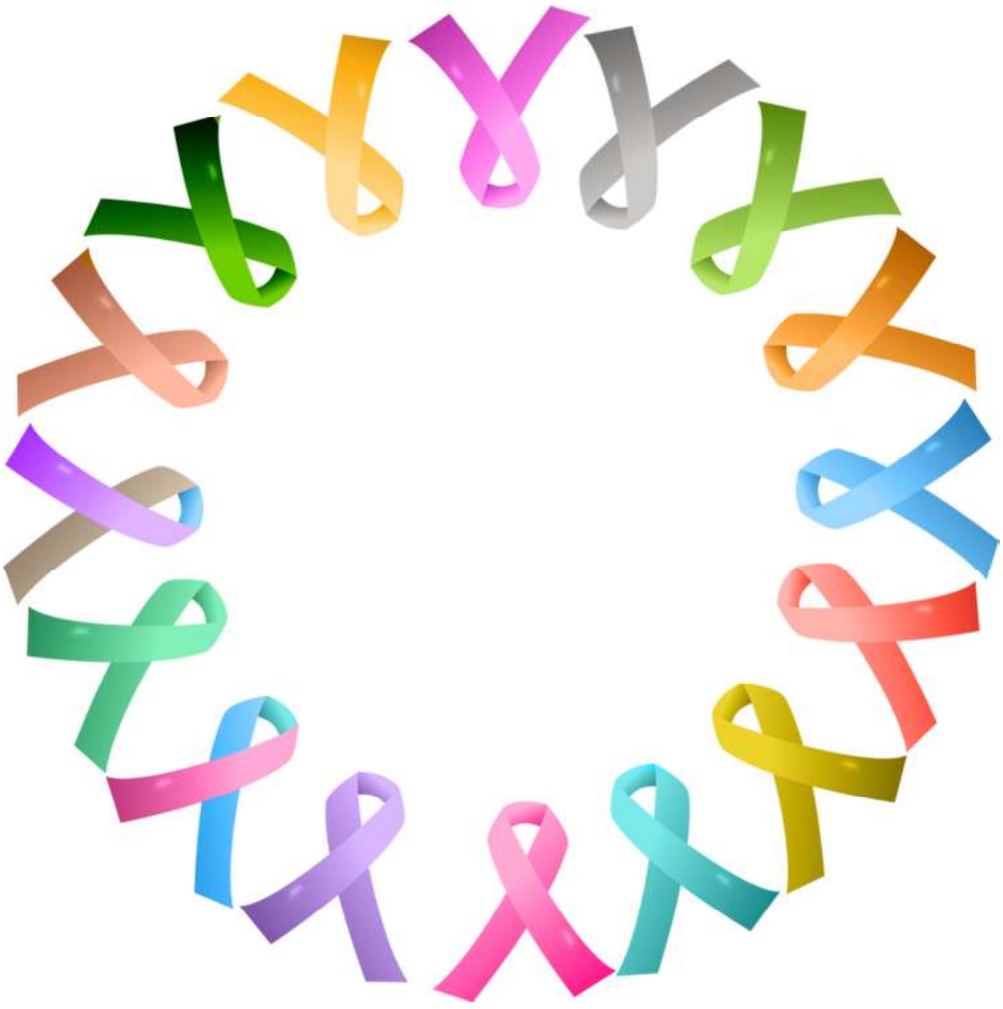

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oncogenic Δ40p53β and a decrease in tumor-suppressive TAp73β. Finally, we have studied the expression profile of the p53/p73 isoforms in a panel of five patient-derived melanoma cell lines that harbor mutations in BRAF and show different sensitivity to BRAFi and/or MEKi. We have found that increased levels of p53 isoforms (p53α, p53β, and Δ40p53β) and lower levels of tumor-suppressive TAp73β isoform could correlate with acquired resistance to BRAFi/MEKi and/or BRAFi targeted therapy. We, therefore, propose that p53 family isoforms can play a role in melanoma cells' aggressiveness and could be a potential marker and target for melanoma therapy.
Keywords: isoforms, melanoma, p53, p73, resistance, targeted therapy

O07

The anticancer effects of triterpene saponin deglucocyclamine isolated from *Cyclamen hederifolium*

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Background: Following the traditional Serbian use of cyclamen tubers in the treatment of the most aggressive forms of lung cancer, we performed methanolic extraction of fresh tubers of Cyclamen hederifolium to isolate and identify bioactive constituents. The triterpene saponin deglucocyclamine (SDGC) was identified as a major constituent of cyclamen extract, and its anticancer effects were studied using a panel of NCI-60 cell lines and primary cell cultures obtained from patients with non-small cell lung cancer (NSCLC). **Material and Methods:** The cyclamen tubers were ground, lyophilized, and extracted with methanol at room temperature with the use of an ultrasonic bath. The part of the methanol extract was further fractionated by dissolving in H2O and then washed with CH2Cl2. The water layer was extracted with n-BuOH. The butanol extract was fractionated by isocratic CC on silica gel with CHCl3−MeOH−H2O eluent. This resulted in the isolation of triterpene saponin deglucocyclamine (SDGC, C52H84O22) which was identified using 1D and 2D NMR spectra. SDGC was tested at 10 μM against a panel of NCI-60 cancer cell lines and then over a concentration range of 0.01-100 μM using the sulforhodamine B (SRB) assay. SDGC was also tested in the 0.01-10 μM concentration range against 5 primary patient-derived NSCLC cell cultures (2 stage IB, 2 stage IIA, and 1 stage IIB) using the MTT assay. Cell death analysis was performed in patient-derived NSCLC cells using annexin/propidium iodide staining and flow cytometry. **Results:** SDGC at 10 μM after 72 h significantly inhibited cell growth of all tested cancer cell lines in the NCI-60 panel. Therefore, SDGC IC50 values were evaluated across the entire NCI-60 panel, ranging from 600 nM to 1 μM. In patient-derived NSCLC cells, SDGC IC50 values were between 1.3 μM and 4.6 μM after 72 h of treatment. SDGC at 10 μM induced late apoptosis and necrosis, significantly reducing the percentage of viable cells to 40% after 48 h. At the same concentration, cisplatin was ineffective against patient-derived NSCLC cells. **Conclusion:** The triterpene saponin deglucocyclamine (SDGC), whose anticancer effects have not been studied before, showed promising results against NSCLC, melanoma, colon, breast, ovarian, kidney, prostate, and CNS cancer cell lines, as well as patient-derived NSCLC cells. Further more detailed studies of SDGC at the cellular and molecular level are planned.
Keywords: anticancer, cyclamen, NCI-60, non-small cell lung carcinoma, patient-derived cell culture

O08

The effect of diiron thiocarbyne complex on tumor cells of different grade

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Background: Iron is an important trace element with a broad range of functions in diverse physiological processes and a tightly regulated metabolism. Over the years, numerous studies have indicated that cancer cells exhibit an iron-seeking phenotype, meaning they have higher demands for iron than healthy cells. This feature may serve as a foundation for a new approach to cancer therapy. In order to develop an anticancer drug with improved efficacy,

higher selectivity and reduced toxicity, a new organo-diiron complex with a bridging thiocarbyne ligand (FeSDAP) was synthesized. **Material and Methods:** The cytotoxic effect of FeSDAP was investigated on mouse cancer cell lines (B16-F1 low-invasive melanoma, B16-F10 high-invasive melanoma and 4T1 breast cancer), as well as on mouse embryonic fibroblasts (NIH-3T3). For investigation of its mechanism of action, flow cytometry and light microscopy were used. To investigate how 72h long exposure to DMAP *in vitro* affects the potential of B16-F1 and B16-F10 cells to form tumor in vivo, respective subcutaneous synegenic models in C57BL/6 mice were used. **Results and Conclusions:** Treatment with FeSDAP decreased viability of all cells after 72 hours, with significantly less potent effect on embryionic fibroblasts compared to cancer cells, suggesting FeSDAP may possess selectivity towards a malignant phenotype. Melanoma cells were almost equally sensitive to the treatment, but more sensitive than breast cancer cells, so both B16-F1 and B16-F10 were selected for further comparative investigation. Treatment with FeSDAP inhibited proliferation of melanoma cells and caused substantial change in their morphology, which was even more pronounced when it comes to B16-F10 cells. After microscopic evaluation, it was shown that melanoma cells went into senescence. Prominent morphological change of B16-F10 cells was caused by transdifferentiation into Schwann Cell-Like Cells. Further investigation of tumorigenic potential of treated melanoma cells in mice showed that the average tumor size in the groups that received treated cells was significantly smaller, suggesting that melanoma cells have persistently reduced potential to form tumor after single in vitro treatment with FeSDAP. Ultimately, these results strongly indicate that investigated diiron thiocarbyne complexes may display a promising antitumor potential that will be investigated in more detail.
Keywords: cell transdifferentiation, cellular senescence, iron compounds, melanoma

O09

The effects of cisplatin-ibuprofen conjugate free and immobilized in mesoporous nanostructured silica on the change of morphology of mouse melanoma cells, and antitumor potential *in vivo*

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Background: Active contribution of cyclooxygenase enzymes (COX) and their products, in particular prostaglandin E2, to tumor progression makesthis enzyme an attractive target for molecular therapy in cancer. The combination of conventional chemotherapeutic drugs with COX1/2 inhibitors, and further enhancement of their delivery into target tissue can be a highly prospective approachin cancer therapy, especially in advanced stages. Accordingly, a cytostatic and anti-inflammatory drug conjugate was synthesised, as well as its immobilization in mesoporous nanostructured silica SBA-15. Detailed evaluation of the cytotoxic potential and the mechanism of action of this conjugate and the appropriate materialon B16 cells was further performed*in vitro*and *in vivo*. **Material and Methods:** Cell viability of B16 melanoma cells was determined by MTT and CV assays. Cell morphologywas estimated byhematoxylin–eosin andOil Red O staining using light microscopy, whilechanges in thenucleiwere validatedby PI staining using fluorescent microscopy. Differentiation of melanoma cells was determined by measurement of tyrosinase activityand the presence of melanin. Syngeneic C57BL/6 mice modelwas used for *in vivo*assessment of the tumorigenic potential of B16 cellsexposed tofree and SBA-15 loaded conjugate*in vitro*, as well as for the evaluation of the antitumor potential of the experimental substances given in the therapeutic regimen. **Results and Conclusion:** Exposure to free or immobilized cisplatin-ibuprofen conjugatedecreasedthe viability of the B16 cell culturewhile morphology of survived cells was changed. Cytoplasm of enlarged and elongated cells showed intensive granularity with enhanced lipid contentand huge irregularly shaped nuclei with prominent heterochromatin foci, all of which indicated senescent state. Increased activity of tyrosinase and the presence of melanin compared to the control, referred to the differentiation of melanoma cells toward primary phenotype.Further inoculation of pretreated B16 cells into C57BL/6 mice showed decreased potential to form tumor incomparison to tumorigenic potential of untreated cells.Additionally, *in vivo* application of free and SBA-15 immobilized conjugatein therapeutic regimentled to statistically significant reduction of tumor volume, with only fewer signs of toxicity compared to cisplatin as positive control.New knowledge about this compound and corresponding materialis reflected in their antitumor potential on mouse melanoma cells, which opens numerous possibilities for further research.
Keywords:cell differentiation, cisplatin, ibuprofen, melanoma, nanoparticles, senescence