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## PROCEEDINGS

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# LS4.001-Invited
# Translation of killing based into differentiation based therapy of malignant diseases using nanotechnology: Getting out of the vicious circle.

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There is growing evidence about tumor promoting features of dying cells in advanced tumor tissue. Crosstalk between dying and surrounding cells often leads to tumor repopulation, local immuno-suppression and metastasis. Consequently, resistance to chemotherapy is rather connected to proliferative response to cell death induced by the therapy than to development of apoptotic resistant phenotype of individual cell. As an alternative approach that will avoid chemotherapy induced tumor repopulation, induction of cell differentiation emerges. Until today, different naturally/synthetic compounds able to convert non/low differentiated malignant cell into less invasive or normal cell like phenotype have been discovered. It was also found that not just the type of the drug, but also dynamic of drug delivery, can define its action and replace cell death induction with non-aggressive tumor suppression.

Objectives: This lecture will give insight into usage of SBA-15 mesoporous silica nanomaterial as a biocompatible drug carrier of metal based chemotherapeutics in terms of improved stability, drug efficacy, and conversion of killing-based to differentiation-inducing property.

Material and methods: Antitumor effect of SBA-15 mesoporous silica nanoparticles loaded with organotin(IV) compound has been evaluated on two melanoma cell lines - less invasive B16 mouse and highly aggressive, anaplastic human melanoma cell line - A375 and singeneic model of melanoma in C57BL6 mice. Cell viability has been determined by MTT and CV. Cell death, proliferation, senescence and production of reactive oxygen/nitrogen species have been estimated by Flow cytometry. Biochemical assays, light microscopy and TEM were used for detection of melanoma cell differentiation. The protein expression relevant for stem maintenance has been assessed by WB.

Results: Melanoma cells internalized drug loaded nanoparticles after 2 h of incubation through passive fluid-phase uptake and macropinocytosis, thus leading to later phenotype changes and loss of malignant potential in both- B16 and A375 cells. In contrast to free immobilized compound induced cell differentiation, an effect previously unknown for metal-based drugs and nanomaterial alone. The strong therapeutic potential was achieved in lower dose range than in the case of the free drug, reflected on morphological, biochemical and ultra-structural features of treated melanoma cells. While anaplastic A375 cells lost stemness and became senescent, B16 cells differentiated into more mature, melanocyte like phenotype. Abolished tumor growth observed in syngeneic model *in vivo* confirmed *in vitro* obtained data, showing that applied treatment was safe and highly efficient.

Conclusion: In opposite to free drug, organotin(IV) compound loaded into mesoporous silica SBA-15 nanocarriers induced melanoma cell reprograming. In this form agent prevented tumor repopulation as a tissue reactive response to cell damage, opening the interest for nanotechnology application in nonaggressive treatments of advanced solid tumors.