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193m,195mPt-based nanobioconjugates for combined „chemo-Auger" theranostics of hepatocellular carcinoma (HCC) and HER2+ breast cancer.

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Despite the broad development of medicine for cancer treatment, current therapeutic approaches are not efficient at dealing with aggressive and therapy-resistant neoplasms such as breast cancer or hepatocellular carcinoma. In these tumors, one of the most difficult steps of the therapy process is metastases treatment due to the spread of small size tumors. Targeted therapy with most efficient Auger electrons emitters – 193mPt (30 A.E. per decay) and 195mPt (36 A.E. per decay) - is one of the most promising concept for this approach. Moreover, 195mPt can be easily imaged via SPECT as a result of emission suitable for imaging photons with energy ~98.90 keV. Platinum-based radiopharmaceuticals, due to their relevant characteristics, are encouraging candidates for realizing "chemo-Auger" therapy which should be significantly more effective than typical Auger therapy. Chemotoxicity of platinum can be promoted in highly oxidative environment which occurs in most of hepatic cells and in some of breast/ovarian cancer cells. Biological effectiveness studies of platinum-induced chemotoxicity were realized with two types of nanocarriers – 30 nm core-shell (Au@Pt) and ultra-small 2 nm platinum (PtNPs) nanoparticles, used in forms of HER2+ targeted bioconjugates with Trastuzumab, as well as only polymer-stabilized conjugates for HCC. Research for non-radioactive (bio)conjugates chemotoxicity included evaluation for 2D and 3D in vitro tumor spheroid models. Moreover, one of the main parts was aimed at determining the mechanism of chemotoxicity. There are two different concepts of platinum biological activity. In order to identify the factors responsible for cytotoxic effects, nuclei isolation and oxidative stress markers determination were performed. Obtained results confirmed, that for chemotoxicity of platinum-based nanomaterials, highly oxidative environment is a crucial parameter. Due to presence of naturally occurring increased H2O2 concentration in HCC cells cytoplasm, in this cancer cells significant cytotoxicity was observed at similar level for both - Au@Pt and PtNPs conjugates (~50% at 72h post treatment). Furthermore, our results strongly indicates, that in HER2 overexpressed breast/ovarian cancer cells the oxidative potential is insufficient for inducing cytotoxic effects of platinum. After widely conducted chemical and biological research for non-radioactive conjugates, evaluation with radioactive 193m,195mPt will be performed. Due to very limited availability of high specific activity Pt radionuclides, during subsequent part of research, various direct and indirect ways for high specific activities production will be under investigation.
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Primary author: WAWROWICZ, Kamil (Institute of Nuclear Chemistry and Technology, Dorodna 16, 03-195 Warsaw, Poland)

Co-authors: Dr MAJKOWSKA-PILIP, Agnieszka (Institute of Nuclear Chemistry and Technology, Dorodna 16, 03-195 Warsaw, Poland); Dr SZWED, Marzena (Faculty of Biology and Environmental Protection, University of Lodz, Pomorska 141/143 St,90-236 Lodz, Poland); Prof. BILEWICZ, Aleksander (Institute of Nuclear Chemistry and Technology, Dorodna 16, 03-195 Warsaw, Poland)

Presenter: WAWROWICZ, Kamil (Institute of Nuclear Chemistry and Technology, Dorodna 16, 03-195 Warsaw, Poland)

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