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Nanoteranostics based on multimodal nanoparticles and nanosystems

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Motivation and Aim: Cancer is one of major problems of modern society counting about 15–16 % of all death cases per year and the death toll from cancer continues to rise. Nanotheranostics based on multimodal nanoparticles (NPs) have emerged as one of promising techniques for cancer treatment, which can offer both imaging and therapy modalities [1]. We will highlight our recent achievements in the development of nanotechnologies for nuclear biomedicine, including nuclear medicine and radiology and some important trends in the development of this technology.

Laser ablation has appeared as a new non-chemical pathway for the synthesis of nanomaterials, which is free of limitations of conventional chemical approaches and makes possible the synthesis of ultrapure nanostructures. In this approach, small nanoscale clusters are naturally formed during laser ablation from a solid target, and then released into a liquid ambient to form a colloidal nanoparticle solution. Laser ablation can provide nanomaterials exhibiting unique properties and functionalities.

The properties of NPs as an increased ratio of surface area to volume, the ability of passive/active guidance and high load capacity, a large cross-section of interaction with biological tissues, unique properties of the surface of nanomaterials, easy giving of many functions to nanomaterials, etc. are used. All these properties of laser-synthesized nanomaterials promise their successful employment in theranostics.

We propose silicon (Si) NPs (Si*NPs) synthesized by promising laser-based approaches as a nearly ideal NPs for nanotheranostics [2]. One can use these methods to make stable colloidal dispersions of silicon nanoparticles in both organic and aqueous media, which are suitable for a multitude of applications across the important fields of health care. Size tailoring allows production of Si*NPs with efficient photoluminescence that can be tuned across a broad spectral range from the visible to near-IR by varying particle size and surface functionalization. These applications encompass several types of bioimaging and various therapies, including phototherapy, RF thermal therapy, and radiotherapy [3].

The uniqueness of such Si*NPs is based on their biodegradability, which makes possible rapid elimination of these structures from the organism within several days even if their initial size is large (30–80 nm) under absence of any toxic effects, which was earlier confirmed in a mice model. In addition, in contrast to Si nanostructures prepared by conventional chemical or electrochemical routes, laser-synthesized Si*NPs have ideal round shape, controllable size with low size dispersion, and are free of any toxic impurities, which promises a better transport *in vivo* and the absence of side effects.

Synthesized nanoparticles were tested as carries for promising radionuclides (Re-188, Ga-68) in nuclear medicine, as well as sensitizers in radiation therapy. We demonstrate the possibility for fast PEGylization and conjugation of laser-synthesized Si*NPs with

Rhenium-188 (188Re) radionuclide, which is one of most promising generator-type therapeutic beta-emitters with the energy of positron emission of 1.96 MeV (16.7 %) and 2.18 MeV (80 %) and half-decay time of 17 hours [4]. We show that such conjugates can efficiently deliver the radionuclide through the blood stream and retain it in the tumor region. We also show that Si NPs ensure excellent retention of 188Re in tumor, not possible with the salt, which enables one to maximize therapeutic effect, as well as a complete time-delayed conjugate bioelimination. Finally, our tests on rat survival demonstrate excellent therapeutic effect (72 % survival compared to 0 % of the control group). Combined with a series of imaging and therapeutic functionalities based on unique intrinsic properties of Si*NPs, the proposed biodegradable complex promises a major advancement of nuclear nanomedicine.

Technologies of combined action of various types of radiation (protons-neutrons, protons-carbon ions, multi-ion therapy); targeted proton therapy technologies using promising nanoparticles and systems based on them as therapy sensitizers and active agents for diagnostics.The latter direction involves a significant expansion of the field of modern nuclear medicine through integration with nanotheranostics, which uses nanoparticles for the diagnosis and therapy of cancer, using their unique properties. The introduction of non-radioactive materials that can be activated from the outside using various external sources of nuclear particles to produce radioactivity in situ is one of the new directions of activation of nano-drugs at the site of a cancerous tumor, which can be considered as in situ production of radiopharmaceuticals. Such binary radiotherapy technologies become especially efficient when one can achieve a high tumor/non-tumor action contrast, which enables to minimize side effects related to the irradiation of healthy issues.

Conclusion: Our recent data show that the field of nuclear medicine can be significantly expanded by integrating with nanomedicine, which utilizes nanoparticles (NPs) as carriers of radionuclides or as radiosensitizers for radiation therapy and/or active agents for imaging (radiopharmaceutical medicines in situ). The synergy of nanotechnology with nuclear medicine opens up a new direction of cancer imaging and therapy – nuclear nanotheranostics.

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