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I N Zavestovskaya, M Grigorieva, D Petrunya, A Grigoriev, S M Deyev, P N Prasad, A V Kabashin

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Novel advanced nanotechnologies for nuclear medicine

I N Zavestovskaya^{1,2,<https://orcid.org/0000-0002-2690-6797>}, **M Grigorieva**^{2,1,<https://orcid.org/0000-0003-3759-5186>}, **D Petrunya**¹, **A Grigoriev**¹, **S M Deyev**^{2,3,<https://orcid.org/0000-0002-3952-0631>}, **P N Prasad**^{1,4}
and A V Kabashin^{2,4,<https://orcid.org/0000-0003-1549-7198>}

¹P. N. Lebedev Physical Institute, Leninsky pr. 53, Moscow, Russia

²MEPHI, PhysBio Inst., Kashirskoye shosse, 31, Moscow, Russia

³Shemyakin–Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, Moscow, 117997, Russia

⁴Department of Chemistry and Institute for Lasers, Photonics, and Biophotonics, The State University of New York, Buffalo, New York 14260, USA

⁵Aix Marseille University, CNRS, LP3, Case 917, 13288 Marseille, France

E-mail: zavestovskayain@lebedev.ru

Abstract. Nuclear nanomedicine forms a new research field based on the synergy of nuclear medicine and nanotechnology and implying the use of nanomaterials as carriers of diagnostic or therapeutic radionuclides. Such an approach promises a series of advantages over classical methods of nuclear medicine, including an increased surface area-to-volume ratio, passive/active delivery, high loading capacity, large cross-section in interactions with biological tissues, and unique properties of nanomaterials that make possible many functionalities within one construct. In this short review article, we will highlight our recent achievements in the development of nuclear nanomedicine technologies, which promise the advancement of methods for cancer treatment.

1 Introduction

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. Most problems are related to the fact that methods of early detection of cancer and its metastasis are still insufficiently developed, while surgical intervention and methods of classical therapy are effective only at the early stages of tumor development and cannot guarantee the complete elimination of metastasis.

Nuclear medicine has emerged as one of promising techniques for cancer treatment, which can offer both imaging and therapy modalities. In particular, the therapy modality employs internal radiations from short-living radionuclides to treat rapidly proliferating cancer cells, while normal cells remain unaffected. These radiations cause cytotoxic damage to DNA due to numerous mechanisms, such as the formation of reactive oxygen species, single- and double-stranded DNA breaks, and inhibition of DNA repair mechanisms [1]. The radionuclide therapy becomes especially efficient when one can achieve a high tumor/non-tumor radionuclide contrast, which enables to minimize side effects related to the irradiation of healthy tissues. In a conventional approach, one employs vectoring molecules (specific antibodies, etc.) to target radionuclides to the tumor, but such an approach is not free of problems, including a low loading capacity, side effects and the risk of renal failure.

Profiting from new properties of materials at the nanoscale, nuclear nanomedicine has emerged as a new promising field, which utilizes nanoparticles (NPs) as carriers of radionuclides [2,3]. When functionalized by appropriate biopolymers, nanoparticles promise safe and controllable transport of radionuclides in the blood stream, as well as a passive vectoring mechanism for targeting tumors [4]. In



addition, nanoparticles can be more heavily loaded with radionuclides to ensure an enhanced therapeutic outcome in the tumor region.

This short article, we will describe our recent achievements in the development of methods of nuclear nanomedicine to highlight some important trends in the development of this technology.

2 Radionuclides for Nuclear medicine

The type of radionuclide radiation determines its diagnostic or therapeutic nature. The most effective therapeutic radiopharmaceuticals use radioisotopes that emit α - or β -particles, or Auger electrons. The choice of a radionuclide depends not only on its physical properties, but also on many biomedical factors, such as the type and size of the tumor, the density of the target and its heterogeneity [1]. Physical characteristics of the selected radionuclide include the half-life, decay mode and radiation properties of radionuclides. Biochemical characteristics include the need to preserve radioactivity in the tumor, as well as stability and toxicity *in vivo*.

Recent advances in cancer diagnosis and treatment have focused on the development of new radiopharmaceuticals based on targeted delivery. Targeted radiopharmaceuticals are expected to concentrate in the tumor area and selectively destroy cancer cells with a minimum dose of radiation to healthy tissues. This ensures high therapeutic outcome and minimal side effects. In addition, targeting technologies allow one to create theranostic radiopharmaceuticals that simultaneously act as therapeutic and diagnostic tools. In this case, one can profit from approaches of personalized medicine in therapy planning by evaluating individual pharmacokinetic and dosimetry data for each patient.

Promising results were obtained using molecules (antibodies, peptides, etc.) to deliver radionuclides to the tumor [5]. However, since these molecules are small (less than 65 kDa), they can typically carry only a few chelates linked to radionuclide atoms. Consequently, one has to deliver very high concentrations of radionuclide-carrying molecules to achieve a significant therapeutic outcome, but this can cause severe side effects. In addition, the size of the molecular target agents is in the range of renal filtration (< 7-8 nm), which leads to a rapid accumulation of radionuclides in the kidneys to cause renal failure and other problems [6]. One also has to take into account altered profile of bio-distribution and pharmacodynamics when such targeting molecules are used with radionuclides, potential immunogenic effects, etc.

3 Nanoparticles radionuclides delivery systems

Nanomaterials can offer major advantages as carriers of radionuclides, including high surface-to-volume ratio and porous texture, which promises a much higher loading of the carrier by radionuclides. In addition, when functionalized by a proper polymer (polyethylene glycol (PEG), dextran, etc), nanoparticles can have a prolonged circulation in the blood stream and offer a passive mechanism to target tumours based on their selective size accumulation (enhanced permeability and retention (EPR) effect) [4]. Finally, some nanoparticles can have unique properties and provide additional imaging (for example, fluorescence, MRI, photoacoustics, etc. [7]) or therapeutic (for example, photothermal, magnetothermal, PDT, etc.) [8-10] modalities, which can be used in parallel with the nuclear medicine modality.

A variety of nanomaterials have been successfully used in tasks of nuclear medicine as carriers of diagnostic and therapeutic radionuclides, including organic nanoparticles (liposomes, solid-lipid and polymeric nanostructures, etc), gold (Au) nanoparticles, magnetic nanoparticles (Fe_3O_4 , CoFe_2O_4 , etc), carbon (C) nanoparticles, silica nanoparticles, etc [2,3, 11,12]. In some cases, these nanoparticles made possible the combination of imaging/therapeutic action of radionuclides and additional imaging/therapy option offered by the nanoparticles, including MRI, fluorescence imaging, photothermia, etc.

4 Laser-ablative synthesis of nanomaterials

Despite huge promises of nuclear nanomedicine approaches, this field has seen limited success, primarily because of a lack of nanocarriers, which are safe, excretable and have favorable pharmacokinetics to efficiently deliver and retain radionuclides in a tumor. One of main problems is related to the fact that conventional chemical synthesis typically leads to the contamination of formed

nanomaterials by hazardous products causing toxicity effects. Another problem is related to weak excretion of many nanomaterials (even highly biocompatible), which leads to their residual accumulation and possible toxicity effects.

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 [13]. In this approach, small nanoscale clusters are naturally formed during laser ablation from a solid target, and then released either into a gaseous ambient to form a nanostructured film on a substrate [14] or into a liquid ambient to form a colloidal nanoparticle solution [15,16]. Since laser ablation can be performed in ultraclean environment, it can provide exceptional chemical purity of nanomaterials, typically not possible via conventional chemical pathways. In addition, laser ablation can provide nanomaterials exhibiting unique properties and functionalities. As an example, laser-synthesized plasmonic Au or TiN nanoparticles are capable of providing photothermal therapy effect [17-19] and SERS-based imaging [20], while laser-synthesized Si nanoparticles can enable fluorescent [21] and non-linear bioimaging [22], hyperthermia-based therapies under radiofrequency [23] and photon [24] excitation. All above-stated properties of laser-synthesized nanomaterials promise their successful employment in nuclear nanomedicine tasks.

5 Safe nuclear nanomedicine: laser-synthesized Si nanoparticles as safe and effective carriers of ^{188}Re radionuclide for cancer therapy

Nanostructured silicon (nanosilicon) occupies a unique niche related to biological systems and biomedical applications. Despite its inorganic nature, this nanomaterial can offer not only excellent biocompatibility, but also biodegradability as in biological environment Si nanostructures decay and excrete from the body with the urine [25]. However, conventional chemical fabrication pathways typically use toxic products and are unable of producing uncontaminated Si nanostructures, which are free of toxicity issues. We recently solved this problem by introducing laser synthesized silicon, which showed no sign of toxicity *in vitro* and *in vivo* [26,27]. Furthermore, after systemic administration in mice model, the nanoparticles gradually decayed and products of decay excreted from the body within days with no sign of side effects [27]. Based on such outstanding properties of laser-synthesized Si nanoparticles, we explored them as carriers of ^{188}Re radionuclide [28], which is considered as one of most promising generator-type therapeutic beta-emitters. As shown in Fig. 1a, the mean size of laser-synthesized nanoparticles was about 2 nm, which is consistent with their good transport *in vivo*. The nanoparticles were then functionalized with PEG and linked to radioactive ^{188}Re atoms (Fig. 1b). The conjugation protocol took only 1 hour, compared to its half-life of 17 hours. When intravenously administered in a Wistar rat model, the conjugates demonstrated free circulation in blood to reach all organs and target tumors, which was radically in contrast with that of the ^{188}Re salt that mostly accumulates in the thyroid gland. We also showed that the nanoparticles ensure excellent retention of ^{188}Re in tumor, not possible with the salt, which enables one to maximize the therapeutic effect. It is important that the conjugate gradually dissolve and excrete from the organism, minimizing the impact of high doses of radiation during first hours after the injection. Finally, as shown in Fig. 1c, our tests on rat survival demonstrated excellent therapeutic effect (72% survival compared to 0% of the control group). Based on successful therapeutic data obtained using conjugates of PEG-coated Si nanoparticles with ^{188}Re radionuclide, we proposed the concept of safe nuclear nanomedicine, which implies the use of highly biocompatible and biodegradable nanomaterials as targeted carriers of diagnostic or therapeutic radionuclides. Such a concept implies a high therapeutic outcome and a complete excretion of the carrier in the absence of any substantial side effects.

In another study [29], we explored the conjugation of laser-synthesized Si nanoparticles with ^{68}Ga , which is one of most promising generator-type radionuclides for positron emission tomography (PET). The conjugation was one via a simple physical adsorption, as many radionuclides have a natural ability to adsorb on silicon oxide (SiO_2) surface [30]. The observed effect was possible due to the fact that laser-synthesized Si nanoparticles have oxide coating (SiO_2), which favored radionuclide adsorption. In another study [31], we further maximized the adsorption of ^{68}Ga on nanosilicon surface by profiting from porous texture of porous silicon and studied biodistribution of Si nanoparticle – ^{68}Ga complexes after systemic administration.

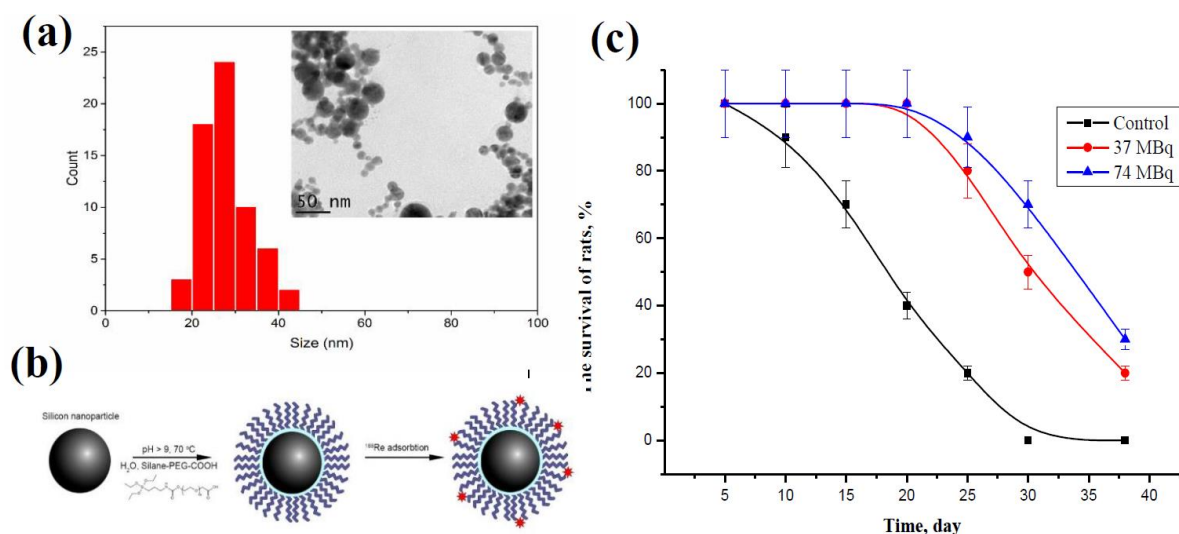


Figure 1. Typical transmission electron microscopy image and corresponding size distribution of Si nanoparticles prepared by laser ablation technique; (c) Schematics of functionalization step to coat Si NPs by polyethylene glycol (PEG) and then decorate it by radioactive ^{188}Re atoms. The total duration of the chemical protocol is less than 30 minutes, which guarantees high activity of ^{188}Re in its end; (c) Survival curves for Wistar rats with implanted cholangioma RS-1 after intratumoral injection of the PEGylized Si nanoparticle - ^{188}Re complexes providing different doses of radioactivity (37 and 74 MBq) and for control group injected with physiological solutions. Adapted from [28].

6 Preparation of nanoformulations labeled with a radioisotope by neutron activation method

We recently proposed that radiopharmaceutical can be obtained in situ by the irradiation by neutron source of a non-radiative nanoformulation, followed by its functionalization [32]. ^{152}Sm isotope can serve as a prominent example. When captured neutrons by a nuclear reaction, ^{152}Sm converts into a short-lived samarium-based radio isotope ^{153}Sm , which is known as one of most promising beta emitters for the treatment of malignant tumors, including lung, prostate and breast cancers. The problem is that it is very difficult to synthesize ^{152}Sm -based nanoformulations in chemically pure, water-dispersible form. We solved the problem by applying methods of femtosecond laser ablation/fragmentation in deionized water to fabricate stable aqueous dispersion of ^{152}Sm -enriched samarium oxide nanoparticles. After a long (300 minutes) laser fragmentation all nanostructures were converted into spherical nanoparticles with energy depended size (increase of laser fragmentation energy leads to decrease of nanoparticle size) [32]. The formed ^{152}Sm -enriched samarium oxide nanoparticles present a prominent object for nuclear medicine.

7 Conclusion

Our recent data show that the field of nuclear medicine can be significantly expanded by integrating with nanomedicine, which uses nanoparticles for the diagnosis and therapy of cancer. Such properties of nanoparticles 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. The synergy of nanotechnology with nuclear medicine opens up a new direction of cancer imaging and therapy - nuclear nanomedicine.

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