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Bioconjugates of barium ferrite as a Ra-223 carriers in alpha-radioimmunotherapy

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Among all alpha particle emitters, only a few nuclides are in considerable interest for alpha-radioimmunotherapy because of their properties, such as half-live, high cytotoxicity and short path length.One of the most important issues, which affects wider use of alpha-radioimmunotherapy in nuclear medicine, is the availability and price of the radionuclides. At-211 is produced by alpha irradiation at high-energy cyclotrons, which are available only in a few scientific centers in the world. Resources of Ac-225 and Bi-213 radioisotope are quite small. On the contrary to Ac-225, Ra-223 (T1/2=11.4d) is already easily (commercially) available. Ra-223 is easily obtained from the Ac-227/Ra-223 generator.

Unfortunately, Ra-223 as va member of Alkaline Earth metals forms very weak complexes. Therefore there is a lack of chelators which can effectively bind Ra-223, retain its daughter radionuclides and be coupled to targeting vectors. We propose to use barium ferrite (BaFe12O19) nanoparticles as multifunctional carriers for Ra-223 radionuclide for alpha-radioimmunotherapy and magnetic hyperthermia.

Barium ferrite nanoparticles labelled with Ra-223 were synthesized with a hydrothermal synthesis method in the autoclave. The reaction mixture of FeCl3, BaCl2 and 223RaCl2 was alkalized with NaOH solution. Next, the reaction mixture was stirred in autoclave at 210oC for 6 h. Obtained radioactive, magnetic [Ra-223]BaFe12O19 nanoparticles were washed with distilled water and hydrochloric acid (1 mM HCl). Yield of labelling was about 70% (for 100kBq Ra-223). Stability of the obtained radioactive nanoparticles was tested in various biological solutions: 1 mM PBS, 0.9% NaCl and in human blood serum. It is confirmed that Ra-223 was highly retained inside nanoparticles in every tested solution. Only about 25% of Pb-211 (decay product of Ra-223) was released to the solution.

Obtained magnetic BaFe12O19 nanoparticles were characterized by transmission emission microscopy and dynamic light scattering. The diameter of synthesized nanoparticles was about 15-30 nm and the determined saturation magnetization of obtained nanoparticles in room temperature was about 42 emu/g.

In order to synthesize a radiobioconjugate having affinity to HER2 receptors, the monoclonal antibody trastuzumab was conjugated to the obtained barium ferrite nanoparticles. Firstly, the surface of barium ferrite nanoparticles was modified with 3-phosphonopropionic acid linker, and then, the monoclonal antibodies were coupled to the barium ferrite nanoparticles using the carbodiimide chemistry.

Synthesized bioconjugate was characterized by thermogravimetric analysis, dynamic light scattering and were tested for stability in biological fluids. The obtained [Ra-223]BaFe12O19-CEPA-trastuzumab radiobioconjugate almost quantitatively retains Ra-223 and majority of the daughter products. Radiobioconjugate has high receptor affinity towards HER2 receptors expressing on ovarian cancer cells and exhibits high cytotoxic effect in vitro (SKOV-3 cell line).

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