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## 212Pb Production and Investigation of a Preparation Based on this Radionuclide for Therapy of Neuroendocrine Tumors

Targeted alpha therapy is actually one of the most promising and rapidly progressing method of treatment of oncological diseases. Of certain interest for radionuclide therapy is 212Pb beta emitter with its daughter nuclides (212Bi and 212Po) undergoing  $\alpha$ -decay which allows one to regard 212Pb as an in vivo generator of alpha-particles.

In this connection, a new method of 212Pb radionuclide production has been developed and implemented for studies in the field of nuclear medicine. Besides, a method of synthesizing a 212Pb-labeled complex based on synthetic peptide Tyr3-octreotate conjugated with bifunctional DOTA chelating agent (DOTATATE) has been implemented. Such compound is specific to SSTR2 type somatostatin receptors whose overexpression is observable in cells of a number of tumors.

Radionuclide 212Pb was produced with the designed 228Th/212Pb generator. The operation principle of the generator is based on the transfer of gaseous 220Rn by airflow from a vessel with the 228Th-containing ion exchange resin into a separate collector vessel. The 220Rn decay results in the formation of 212Pb which is washed out from the collector by 0.1M HCl solution. Such phase separation ensures high radionuclide purity of the preparation which is of high significance for its application in nuclear medicine. 228Th/212Pb generator design allows generating 10-20 mCi of 212Pb in small volume. Every cycle of the 212Pb radionuclide production lasts for 72 h.

Dependences of the yield of the DOTATATE labeling reaction with 212Pb radionuclide have been studied in cases of different peptide masses in the reaction mixture. The specific activity of preparation varied starting from 0.025 MBq/nmol of peptide and higher. The results of the 212Pb-DOTATATE synthesis efficiency depending on the synthesis duration and pH variety will also be presented. In particular, in case of low specific activities one can attain high labeling yield (>95%) at the synthesis temperature of 90  $^{\circ}$ C, the synthesis duration of 30 min and pH values of 6.0-6.5.

Dissociative stability of the synthesized preparation in isotonic solution has also been studied. It was shown that the complex retains its integrity at the level of more than 90% throughout the 212Pb half-life (10.64 h). Also experiments to determine the complex stability in human blood serum were made. Serum was sampled from blood of a healthy volunteer. After holdup of the preparation in blood serum during different time intervals, serum proteins were denatured followed by centrifugal protein precipitation. The degree of stability was estimated from the ratio of protein-unbound activity to the initial activity in corresponding aliquot. The experiments have proven that throughout all of time up to 10 h the stability is at the level of 80-85%.

Researches of the 212Pb-DOTATATE cytotoxicity were also performed on rat pancreas cancer cells (Rin-m5F cell line) by MTT assay. Receptor binding studies of the synthesized complex are also intended to perform. In the long term, biodistribution investigations and other preclinical studies are also planned to carry out.

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