Contribution ID: **180** Type: **Verbal**

Modified Inorganic Nanoparticles as a Vehicles for Alpha Emitters in Radionuclide therapy

Tuesday, 13 May 2014 16:00 (15 minutes)

Alpha particle emitting isotopes are in considerable interest for radionuclide therapy because of their high cytotoxicity and short path length [1]. Unfortunately, all available emitters have serious disadvantages: 211At forms weak bond with carbon atoms in the biomolecule and in the case of 212Bi, 213Bi and 226Th short half-life often limits the application of these nuclides. However, the short half-life of 212Bi and 213Bi could be effectively lengthened by binding the parent radionuclide 212Pb (t1/2 = 10.6 h) or 225Ac (t1/2 = 10 d) to a biomolecule, thereby effectively extending the use of short half-life 212Bi and 213Bi. In addition, in vivo generator delivers much greater dose per unit of administered activity compared to 212Bi and 213Bi alone. Also three radium radionuclides 223Ra, 224Ra and 225Ra exhibit very attractive nuclear properties for radiotherapy, but the lack of appropriate bifunctional ligand for radium was the reason why these radionuclides did not find application in receptor targeted therapy. In our studies we investigated the use of TiO2 nanoparticles as potential carriers for 225Ac/213Bi in vivo generator and nanozeolite particles as vehicles for 223,225Ra radionuclides.
The TiO2 nanoparticles have unique properties like: high specific surface, high affinity for multivalent cations and simple way of synthesis, which are useful in the process of labelling. Commercially available (e.g. P-25 Degussa) and synthesised in our laboratory nanoparticles were used in experiments. The nanoparticles were characterized by TEM, SEM, DLS and NanoSight techniques.
In our experiments we tested two different methods of labeling. The first one was based on the possibility of formation strong bonds with certain cations on the surface of the nanopraticles. In the second one, TiO2 nanoparticles were doped with 225Ac during the process of synthesis. In both cases we obtained high yields of labelling (>99%).
Afterwards, the stability of labelled nanoparticles was examined in 0.9 % NaCl, 10-3 M EDTA, solutions of biologically active substances (cysteine, glutathione) and human serum. In case of TiO2 nanoparticles labelled with Ac-225, which was built in the crystalline structure, the leakage of 225Ac and its daughter radionuclides was not significant in any of solutions, even when the incubation time was extended to 10 days. In the case of nanoparticles with adsorbed 225Ac on surface the leakage in serum was slightly higher, but still insignificant.
Also the NaA nanozeolite as a carrier for radium radionuclides has been studied. 223Ra, and 225Ra, the α-particle emitting radionuclides, have been absorbed in the nanometer-sized NaA zeolite through simple ion-exchange. 223,225Ra-nanozeolites have shown very good stability in solutions containing: physiological salt, EDTA, amino acid and human serum. To make NaA nanozeolite particles dispersed in water their surface has been modified with silane coupling agent containing poly(ethylene glycol) (PEG) molecules.
To obtain conjugates specific for receptors on glioma cancer cells short peptide substance P were covalently attached to the PEG-TiO2 and PEG-nanozeolite surface. The obtained bioconjugate were labeled with 225Ac and 223Ra respectively. The serum stability of labelled biconjugates was similar or little better than unmodified nanoparticles. The cell affinity, cytotoxicity and biodistribution studies of the obtained radiobioconjugate are in progress.

References

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Acknowledgments

This work was supported by National Science Center of Poland (Grant 2011/01/M/ST406756)

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Session Classification: Radiopharmaceutical Chemistry, Labelled Compounds 1

Track Classification: Radiopharmaceutical Chemistry, Labelled Compounds