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Actinium Biokinetics and Dosimetry: What is the Impact of Ac-227 in Accelerator-Produced Ac-225?

Among the growing list of alpha-emitting isotopes now available for pharmaceutical development, Ac-225 can act as an in vivo alpha-generator radionuclide and is of great interest for new targeted alpha-therapy applications. To seek further development of Ac-225 bioconjugate therapeutics, ongoing efforts aim at addressing current limitations, including lacking supply of the radioisotope, insufficient understanding of its biodistribution and biodosimetry, poor retention of alpha-emitting daughter products at the target site, as well as inadequate chelation, one of the major drawbacks.

The U.S. Department of Energy's Isotope Program has been exploring new pathways for the production of the radioisotope Ac-225 at accelerator facilities to address a potential increased need for medical applications. However, the presence of co-produced, long-lived Ac-227 (21.8 y half-life) is observed in about 0.15-0.3 activity percent in the accelerator-derived product at the end of target bombardment. Up to 0.5 activity percent values due to Ac-227 could be anticipated in a research/clinical setting. One goal of our work is to delineate the biodistribution of Ac-225, its short-lived daughter products, and potential trace contaminants such as Ac-227 that may be co-produced in new larger-scale accelerator-derived processes. The biokinetics of unchelated, chelated (with classic macrocyclic structures, amino-polycarboxylic acids, or new hydroxypyridinone ligands under development), and bio-conjugated Ac-225 and Ac-227 were determined in several mouse models. The resulting biodistribution and dosimetry profiles highlight significant differences among isotope and ligand combinations that must be considered and addressed in order to ensure bioconjugated Ac-225 is safe for use in the clinic.

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