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Production and chelation of alpha-emitting radiometals for targeted alpha therapy (TAT)

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Coupling alpha-emitting radionuclides with disease seeking targeting vectors for site-selective delivery of cytotoxic radiation has the potential to be a powerful technique for treating metastatic and hard to treat cancers. The success of this type of treatment, termed targeted alpha therapy (TAT), is reliant on the availability of isotope and ability to securely tether said isotope to a biomolecule of interest. With four alpha particles in its decay chain, actinium-225 (^{225}Ac ; $t_{1/2} = 9.9$ d) is a promising candidate isotope for TAT. Similarly, the single alpha-emitter lead-212 (^{212}Pb ; $t_{1/2} = 10.6$ h) has generated significant interest as a matched theranostic pair with ^{203}Pb ($t_{1/2} = 51.9$ h), compatible with single-photon emission computed tomography (SPECT) imaging. The current limited global supply, and lack of appropriate chelating ligands (molecules used to bind the isotope to the biomolecule) has delayed the advancement of TAT-drugs towards the clinic. Herein, we describe efforts to produce, purify, and evaluate the radiolabeling ability of ^{225}Ac and ^{212}Pb , by leveraging TRIUMF's unique infrastructure (located in Vancouver, Canada). For ^{225}Ac , the ISAC isotope separation on-line (ISOL) facility, as well as the 500 MeV cyclotron were used to produce preclinical and clinical amounts of isotope, respectively. For ^{212}Pb , a ^{228}Th generator was manufactured.

^{225}Ac alongside parent nuclide radium-225 (^{225}Ra ; $t_{1/2} = 14.8$ d) were produced via spallation of uranium carbide targets with 480 MeV protons on ISOL's radioactive beam facility. Downstream from the target, a high-resolution mass separator was used to isolate ^{225}Ra and ^{225}Ac ions from other isotopes produced in the spallation process. Implantation resulted in isolation of 1.0 – 7.5 and 1.4 – 18.0 MBq of ^{225}Ra and ^{225}Ac , respectively. The implanted activity was etched off the sample stage with dilute acid, and ^{225}Ac was separated in >99% yield from ^{225}Ra using solid phase extraction (DGA resin). This method has resulted in the isolation of MBq quantities of both ^{225}Ra and ^{225}Ac , where the former can be stored and used as a generator for ^{225}Ac . Clinical scale-production via irradiation of ^{232}Th targets on the 500 MeV cyclotron resulted in ^{225}Ac products suitable for our studies. Conveniently, the by-products produced during spallation can be extracted to prepare a $^{228}\text{Th}/^{212}\text{Pb}$ generator that can deliver up to 9 – 10 MBq of ^{212}Pb daily. Subsequently, ^{225}Ac and ^{212}Pb coordination properties with a library of chelating ligands along with commercial standard DOTA were evaluated by testing radiolabeling efficiency, and complex stability.

In conclusion, we have successfully established a production method for ^{225}Ac which yields activities adequate for pre-clinical screening (^{225}Ac via ISOL, or ^{212}Pb via ^{232}Th spallation) or clinical production (^{225}Ac via ^{232}Th spallation). Furthermore, several novel radiometal-chelators showed promising radiolabeling properties and kinetic inertness *in vitro* compared to commercial standards and will be tested *in vivo* in future studies.

(1) Robertson, A. K. H. et al. *Curr. Radiopharm.* 2018, 11 (3), 156–172. <https://doi.org/10.2174/1874471011666180416161908>.

(2) Ramogida, C. F.; et al. *EJNMMI Radiopharm. Chem.* 2019, 4 (1), 21. <https://doi.org/10.1186/s41181-019-0072-5>.

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