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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 (²²⁵Ac; t_{1/2} = 9.9 d) is a promising candidate isotope for TAT. Similarly, the single alpha-emitter lead-212 (²¹²Pb; t_{1/2} = 10.6 h) has generated significant interest as a matched theranostic pair with ²⁰³Pb (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.¹ Herein, we describe efforts to produce, purify, and evaluate the radiolabeling ability of ²²⁵Ac and ²¹²Pb, by leveraging TRIUMF's unique infrastructure (located in Vancouver, Canada). For ²²⁵Ac, 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 ²¹²Pb, a ²²⁸Th generator was manufactured.
²²⁵Ac alongside parent nuclide radium-225 (²²⁵Ra; 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 ²²⁵Ra and </sup>225</sup>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 ²²⁵Ra and ²²⁵Ac, respectively. The implanted activity was etched off the sample stage with dilute acid, and ²²⁵Ac was separated in >99% yield from ²²⁵Ra using solid phase extraction (DGA resin).² This method has resulted in the isolation of MBq quantities of both ²²⁵Ra and ²²⁵Ac, where the former can be stored and used as a generator for </sup>225</sup>Ac. Clinical scale-production via irradiation of </sup>232</sup>Th targets on the 500 MeV cyclotron resulted in ²²⁵Ac products suitable for our studies. Conveniently, the by-products produced during spallation can be extracted to prepare a ²²⁸Th/²¹²Pb generator that can deliver up to 9 – 10 MBq of ²¹²Pb daily.³ Subsequently, ²²⁵Ac and ²¹²Pb 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 ²²⁵Ac which yields activities adequate for pre-clinical screening (²²⁵Ac via ISOL, or ²¹²Pb via ²³²Th spallation) or clinical production (²²⁵Ac via ²³²Th 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.

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