Mass separation of ^{225}Ac from ^{227}Ac and from irradiated Th targets to support Targeted Alpha Therapy

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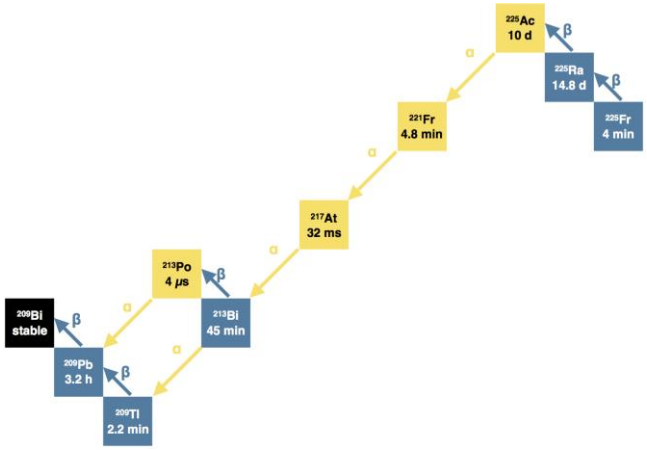
Max 2 pages from Introduction to References and Funding

Introduction & background: (state of the art and goal/motivation for the project)

Targeted Alpha Therapy (TAT) is a very promising approach for cancer treatment in nuclear medicine [1]. It suffers however greatly from the difficult access to suitable α-decaying isotopes so that only one radiopharmaceutical for α therapy has currently received FDA approval, namely $^{223}RaCl_2$ under the brand Xofigo®.

The isotope ^{225}Ac is a very promising candidate for TAT as its decay chain features four α particles in close succession – see figure. Its half-life ($T_{1/2}$ 9.92 days) is also well suited for linking to a large variety of pharmaceuticals, such as peptides, antibodies and antibody fragments.



Moreover, this isotope may also be considered as a generator for ^{213}Bi [2], which is a complementary α emitter with a much shorter half-life ($T_{1/2}$ 45.6 min) that is better suited for radiopharmaceuticals with a quick clearance in the body, such as nanobodies and peptides [3].

The efficacy of ^{225}Ac for TAT has been demonstrated already in several pre-clinical studies and even in clinical trials, e.g. [4]. Further developments and a path towards regular clinical use are however greatly limited by the short supply for this isotope, currently only available from stockpiles resulting from the XXth century nuclear weapon and nuclear engineering research as the decay product of ^{229}Th, itself coming from the decay of ^{233}U.

Alternative production routes are being explored [5], such as ^{226}Ra(p,2n)^{225}Ac – which is then limited by the availability of the radioactive target material ^{226}Ra and the complexity of handling ^{222}Rn, or ^{232}Th(p,x)^{225}Ac. While the latter approach benefits from easier access to the target material, it suffers from co-production of ^{227}Ac contamination ($T_{1/2}$ 21.773 years) [6], which would render any ^{225,227}Ac radiopharmaceutical improper for distribution in many countries due to the waste managing issues. Mass separation between A=225,227 is therefore required in the case of such production.

Project description: (detailed description of the project, translational, pre-clinical, imaging, treatment, new method)

In this project, we shall demonstrate the full feasibility of mass separation of ^{225}Ac from ^{227}Ac from irradiated ^{232}Th targets. The CERN MEDICIS facility is uniquely suited to test the mass-separation protocol. The sample material is heated to high temperature (up to 2000°C) to induce the diffusion and effusion of the radioisotopes. The radioisotopes are then ionized in

the ion source, accelerated to an energy of 30-60 keV, and analyzed according to their mass-over-charge ratio via a 70° dipole magnet. The isotopes of interest are collected at the end of the beam line onto a substrate appropriate for further radiochemical preparation.

In this project, we shall import ^{225,227}Ac samples to CERN MEDICIS from TRIUMF (Vancouver, BC, Canada) either chemically separated or within an irradiated target. The sample shall then be introduced into a MEDICIS target & ion source unit and installed at the MEDICIS front end to study the mass separation process. The biggest uncertainties in this process are the **release properties** from the target material (sample form), the **ionization efficiency** of actinium, and the **purity of the final sample**. The transport efficiency from the ion source to the final collection as well as the mass resolving powers are well under control.

Materials and Methods: (planned experiments, where, licences for radioisotopes/animals, timeline)

Target material & irradiation at TRIUMF: TRIUMF will perform irradiation of metal thorium target at the end of beamline 1A (500 MeV, ~50 µA). Irradiation tests will be performed from several hours to several days, depending on the quantity needed to produce a relevant ^{225}Ac/^{227}Ac mixture [5]. Furthermore, radiochemical separation will be performed at TRIUMF, followed by sample characterization by γ spectroscopy, and finally the samples of ^{225}Ac/^{227}Ac fractions will be shipped to CERN MEDICIS for testing mass separation. Alternatively, mixtures of ^{225}Ac/^{227}Ac can also be premade from various sources. Irradiated targets without processing can also be shipped to CERN MEDICIS to study the feasibility and efficiency of isolating ^{225}Ac from an irradiated target. Different chemical forms of thorium can be tested for irradiation, including thorium oxide, carbide etc. This irradiation can be performed within regular operation of the main cyclotron from May to December.

Ionization investigation at CERN MEDICIS: Actinium has not been collected at CERN ISOLDE via surface ionization. However, laser resonance ionization schemes have been developed at TRIUMF [7], have been studied in details in TRIUMF and LISOL [8-9], and have recently been demonstrated at CERN ISOLDE [10]. The different conditions in terms of operation, sample release, and ion source load will however require to investigate how to optimize the operation to maximize the efficiency and make this approach viable for large-scale production. The existing MELISSA laser facility at MEDICIS is adequate for the ionization of actinium [11]. Molecular release of diatomic Ac-halogen may be investigated.

Radiochemical characterization at SCK•CEN: The sample will be characterized at SCK·CEN by first dissolving the Zn layer off the Au foil and analyzing the Zn concentration by ICP-MS.[1] The ^{225}Ac activity and potential impurities will then be investigated by γ spectrometry. Finally, the remaining Au foil will also be dissolved and analyzed for ^{225}Ac to study whether the ^{225}Ac penetrated beyond the Zn foil. Additionally, the residual activity of ^{227}Ac after full ^{225}Ac decay will be measured by α spectrometry to allow a conclusion about the efficiency of the mass separation.

References and Funding: (literature, funding of project, other projects/grants linked)

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[4] C. Kratochwil et al., *^{225}Ac-PSM-617 for PSM-targeted α-radiation therapy of metastatic castration-resistant prostate cancer*, The Journal of Nuclear Medicine **57** (2016) 1941-1944.

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Isotope requests: (which isotope, activity, number of deliveries over period, purity grade)

Mass separation of ^{225}Ac from ^{225}Ac/^{227}Ac samples from TRIUMF;

- Min 10 MBq of ^{225}Ac with min 1 MBq of ^{227}Ac per sample prepared from separate sources (accumulated ^{227}Ac & ^{225}Ac from ^{229}Th decay);
- Irradiated Th metal samples with higher activities (up to 10x) once to twice a year – operation May to December each year;
- Development of ThO target for future irradiations.

Shipment of the ^{225}Ac samples to SCK•CEN for radiochemical analysis:

- Min activity desired ~1 MBq
- Sample format: Zn-coated Au layer

Additional note: the success of this project would herald the availability of ^{225}Ac – and consequently ^{213}Bi – at CERN MEDICIS for further research projects.