EUROPEAN ORGANIZATION FOR NUCLEAR RESEARCH

Proposal to the ISOLDE and Neutron Time-of-Flight Committee

Towards reliable production of ^{225}Ac for medical applications: Systematic analysis of the production of Fr, Ra and Ac beams.

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Abstract: In this proposal, we propose the investigation of the release curves and yields of $^{205,207,218-228}$Fr and $^{214,219-228}$Ra together with ^{225}Ac with UCx targets and surface and laser ionization ion sources at ISOLDE. The production of pure ^{225}Fr and ^{225}Ra beams using the ISOL technique can be used as generators of ^{225}Ac/^{213}Bi for targeted alpha therapy trials. Recent developments in the resonance laser ionization scheme of Ra and the capabilities of producing intense beams of Fr and Ra from a thick UCx target, allow for the characterization and optimization of ^{225}Fr and ^{225}Ra production for medical applications. We also propose the direct production of Ac beams.

Requested shifts: 6 shifts, (split into 2 runs over 1 year)

1 Context

The use of radionuclides for diagnosis and treatment in medicine has become a common practice over the past century. A lot of progress has been achieved with the development of positron emission tomography (PET) using ^{18}F with the glucose analog ^{18}FDG. Furthermore, there are important developments towards targeted radionuclide therapy. One of them is the marketing of alpha-emitting radiopharmaceuticals, e.g. Xofigo® based on $^{223}RaCl_2$ salt for hormone resistant prostate cancers with bone metastasis. The marketing of new radiopharmaceuticals means one has to start testing the compounds on animal models before performing clinical trials to test the efficacy, toxicity, side effects and precise prescription dose of the drug on the patient. Before marketing these new radiopharmaceuticals, the development itself is an intensive process. One has to identify biological receptors or targets, synthesize suitable compounds and synthesize and purify the radioisotope.[1, 2]

Over the past years, the interest for new radioisotopes in nuclear medicine has significantly grown, more specifically low range beta emitters, e.g. ^{177}Lu, alpha emitters, e.g. ^{213}Bi, and Auger electron emitters, e.g. ^{117m}Sn. These radioisotopes can bring a solution when other approaches cannot be used, e.g. chemotherapy, surgical resection and external radiotherapy. Targeted alpha-therapy (TAT) has the potential to be such a solution.[1]

In TAT, alpha-emitting radionuclides encapsulated in a chemical coordination complex are transported to the target by an appropriate pharmaceutical drug. Here, the radionuclide decays, releasing the alpha particle. Due to its high linear energy transfer (LET) value, the energy of the alpha-particle is deposited over a very short path of only 70 to 100 μm, with a very dense ionizing track. Therefore, most of the alpha particle energy is deposited within microscopic tumor cell clusters while doses to the surrounding healthy tissue are limited. The double stranded breaks in the DNA produced by the alpha particle are more difficult to repair for the tumor repair mechanisms. Therefore, TAT can be expected to be very efficient to kill tumor cells. Tests are already ongoing for a few specific applications of TAT, e.g. treatment of recurrent brain tumor, recurrent ovarian cancer, myelogenous leukemia and others.[1, 3]

Some of these promising alpha emitting radioisotopes are ^{225}Ac and its daughternuclide ^{213}Bi. Early biomedical studies by Beyer *et al.* in the 1990's using ^{225}Ac, produced at ISOLDE, investigated the influence of the concentration of a chelating ligand, EDTMP (EthyleneDiamineTetraMethylenePhosphonic acid), on the bio-distribution of simultaneously injected radioisotopes of rare earth elements and ^{225}Ac [4]. Today, more medical studies using both ^{225}Ac and ^{213}Bi are ongoing. Up to now, promising results from clinical trials treating glioblastoma, hormone resistant prostate cancer with metastasis, neuroendocrine tumors resistant to chemo- or radiation therapy have been reported. In 2014, the successful treatment of bladder cancer by targeted alpha therapy using 370 MBq of ^{213}Bi has been published [5]. Furthermore, phase I/II trials were performed for the efficacy of ^{213}Bi on acute myeloid leukemia. It was concluded that these trials provide the rationale for the use of targeted alpha therapy for small volume types of leukemia and cancer [6]. Bodet-Milin *et al.* [7] list some of the ongoing studies on radioimmunotherapy of acute leukemia. The studies mentioned here are obviously not an exhaustive list of all current investigations concerning the use of ^{213}Bi and ^{225}Ac.

2 ^{225}Ac production

In order to be able to perform the necessary studies and trials to allow full scale application of TAT using ^{213}Bi and ^{225}Ac, both isotopes are needed in a sufficient quantity to the research facilities. Today, most of the ^{225}Ac isotopes used for research are milked from the decay of ^{229}Th, which by itself is a decay product of ^{233}U. This ^{233}U is a result of the research, performed in the 20$^{\text{th}}$ century, for civil and military nuclear applications and is produced by the neutron capture of ^{232}Th in a nuclear reactor. Therefore, the availability of ^{229}Th is very limited due to the non-proliferation policy. Furthermore, a lot of impurities are formed in the thorium matrix, e.g. ^{227}Ac. Today, one can also produce ^{225}Ac by proton irradiation of natural thorium via the reaction ^{232}Th(p,x)^{225}Ac. However, here the same problem concerning the impurities of ^{227}Ac is present. The production cross section of ^{227}Ac is about 40% higher compared to ^{225}Ac for a proton energy of 800 MeV [8]. Griswold *et al.* [9] investigated these cross sections for the irradiation with lower energy protons between 78 and 192 MeV. It was found that the effective production cross sections are smaller compared to the high energy protons, but the cross section for ^{227}Ac is still higher or at least equal to that for ^{225}Ac. To limit the radiation dose, there is a high necessity to separate both isotopes before introducing it to the human body. Another method of producing ^{225}Ac is via the irradiation of ^{226}Ra with protons in a cyclotron. However, also this production route has its limitations due to the difficulty of the purification process [10].
It is clear that ^{225}Ac is not publicly available for a lot of research facilities. The limited supply of the isotope is therefore a serious bottleneck for fast progress in the development and marketing of radiopharmaceuticals for targeted alpha therapy using ^{213}Bi and ^{225}Ac. This analysis is supported by different researchers in the field of nuclear medicine as a quote by Elgqvist *et al.* [1] perfectly illustrates. "A major issue that may hamper wide implementation in the clinic and that needs to be simultaneously addressed is the availability of suitable alpha-particle emitters at a reasonable cost. Otherwise, targeted alpha treatment will remain just a potentially effective treatment, or a very rarely implemented option." It is clear that new and pure sources of ^{225}Ac should become available to sustain the increasing demand for research in nuclear medicine.
The production and mass-separation of these isotopes can be achieved using the ISOL technique. Here several possibilities are available. One can opt for the direct production of ^{225}Ac or collect a mother nuclide, i.e. ^{225}Fr or ^{225}Ra, which then decays to ^{225}Ac via beta decay. The production of francium isotopes from uranium-carbide targets in ISOLDE has been adressed by Lukic *et al.* [11] in 2006 based on the ISOLDE SC yields. The ISOL technique has a major advantage in being able to produce a pure beam of each of these isotopes. In that way, one can avoid the difficult chemical separation processes necessary for the purification of the isotopes in current production processes.

3 Yield and release curve characteristics

To optimize the collection of ^{225}Ac from the target, a full characterization of the yield for ^{225}Ac, ^{225}Ra and ^{225}Fr is necessary. The release curves of these elements must be known for an accurate evaluation of the total yield from the ISOLDE target.

One can define the yield of a specific isotope i, Y_i, as the ratio of the ion beam intensity to the primary beam current expressed in ions/μC.

$$Y_i = \frac{N_{0i}}{N_p \times 1.602 \cdot 10^{-19}} \cdot 10^{-6} \int_0^\infty P_i(t, \lambda_i) dt \tag{1}$$

$P_i(t, \lambda_i)$ is the probability density for a radioactive ion, i, with decay constant λ_i to be released and not decayed at a time t. This function includes physical processes like the diffusion of the element in the target matrix, the desorption from the target surface and effusion towards the ion source, where the atom will be ionized. It has been observed that the release starts with a sharp rise. This is followed by a fast drop and finally a slow decreasing tail. An empirical relation has been found to fit this release function using four parameters of which one is a weighing parameter, α, giving the importance of the fast drop and slow tail. The other three are exponential parameters representing the sharp rise, λ_r, fast drop, λ_f, and the long tail, λ_s. Furthermore, it should be normalized to have a total release probability equal to 1. Figure 1 shows the typical form of the release probability function. [12, 13, 14]

$$P_i(t, \lambda_i) = \exp(-\lambda_i t) \cdot \frac{[1 - \exp(-\lambda_r t)] \cdot [\alpha \cdot \exp(-\lambda_f t) + (1 - \alpha) \cdot \exp(-\lambda_s t)]}{\text{Normalisation factor}} \tag{2}$$

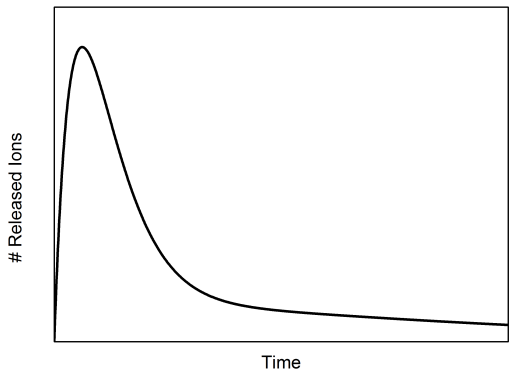

Figure 1: Typical form of the release curve with the sharp rise (λ_r), fast drop (λ_f, α) and finally a long tail (λ_s, α).

4 Measurement techniques and approaches

Determination of the different parameters in the release probability function is a critical step for the efficient determination of the yields of different isotopes. Once the release function of a specific element is known accurately, one does not have to collect that specific isotope for the complete time period over which the isotope is released to calculate the yield. Therefore, it is possible to speed up the process without losing a lot of precision.

For a proper calculation of the release curve parameters for one element, one should measure the release curve of different isotopes of that element. That allows to minimize any influences of the isotope half life or secondary production mechanisms on the release curve. Therefore, we would like to request beam time to measure the release curve for francium using 6 different isotopes, being ^{205,207,220,221,222,227}Fr. Simultaneously, one can measure the release curve for radium using the following isotopes, ^{214,220,221,222,227}Ra. These isotopes, cover a half life range from a few tens of ms to some minutes. This allows an accurate determination of the release curve parameters without the necessity to measure for multiple hours on one single isotope. As one is collecting the above elements for the calculation of the their release curve, yield measurements can be done on more isotopes of these elements. Knowing the release curve, the half life range of the isotopes can be expanded. One can do yield measurements on other isotopes being $^{218,219,223-226,228}$Fr and $^{219,223-226,228}$Ra. Of course, while measuring the release curve of the earlier mentioned isotopes, one can also calculate their yield without the necessity to do extra measurements.
For the alpha emitting isotopes, one can use the well known windmill setup developed by KU Leuven to measure the release curves of the isotopes. This technique will be used for the Fr and Ra isotopes with masses 205, 207, 214, 218 to 224 and 226. For the longer lived isotopes among them, i.e. ^{223,224,226}Ra, one can collect them with the windmill setup and determine the activity offline. For ^{223}Ra, the activity will be measured using ionization chamber (IC) measurements with a chamber provided by National Physical Laboratory (NPL) in the UK. For the other Ra isotopes, which do not yet have a primary standard of radioactivity, the activity will be determined using a combination of gamma spectroscopy and IC measurements at NPL.
The yield measurements for the beta emitters can be performed using the ISOLDE tape station at CERN. More specifically, this will be used for the yield measurements of $^{222-228}$Fr and ^{225,227,228}Ra. The large difference in half life between equal mass isotopes of Fr and Ra can be exploited to discriminate between both elements during the measurements. Again, the long lived isotopes, i.e. ^{225,228}Ra can be collected and analyzed using primary counting methods at NPL.
As francium is an alkali element, its ionization potential is fairly low. Therefore, the proper ion source to be used is a surface ion source. In contrast, radium is an alkali-earth element, thus has a higher ionization potential. One can still ionize it by surface ionization, however, the ionization efficiency is significantly improved using a resonance laser ionization ion source. In the summer of 2016, several resonance ionization schemes for radium were tested by the RILIS team for experiment IS594 at CRIS. The most efficient ionization scheme uses the internal transition between the 7s8s $^3S_1$ and 7s7p $^3P_2$ states. The yield was enhanced by a factor of 3 compared to a Ta surface ion source at 2050 °C [15]. The complete ionization scheme is shown in Figure 2.
The laser ionization of radium isotopes allows a further discrimination between the francium and radium isotopes of equal mass. One can use this to see the difference in ion beam current on a Faraday cup when the lasers are on or off. This is only possible for isotopes which have a high production in the target. Therefore, this technique is expected to work for Fr and Ra isotopes with a mass 220, 221, 223, 224, 225, 226 and 228.
Furthermore, the direct production and release of actinium can be investigated. Due to its relatively large ionization potential of 5.380 eV, surface ionization is not possible. How-

ever, recently extensive research has been done for the development of efficient resonance laser ionization schemes for actinium at the University of Jyväskylä, TRIUMF, University of Mainz and KU Leuven [16, 17, 18]. The knowledge of these ionization schemes opens the possibility to investigate the release of ^{225}Ac from the target. One can measure the release and yield using the windmill and the ISOLDE tape station.

5 Conclusion

For the development of new types of medical treatments, there is a big request for new radioisotopes. Alpha-emitting radionuclides used in targeted alpha-therapy are expected to have a big potential in the future of personalized medicine. More specifically, the focus of medical research is towards ^{225}Ac and one of its daughter nuclides ^{213}Bi. The progress in this investigation is however hindered by the lack of easy processes for the production of pure isotope samples. The ISOL technique can offer a solution to this problem. Using the ISOL method, one has different options for the collection of ^{225}Ac. The first possibility is the extraction of ^{225}Fr, which will decay towards ^{225}Ac by two beta decays via ^{225}Ra. As a second method, one can extract ^{225}Ra from the target. A third possibility is the direct extraction of ^{225}Ac from the target. This last method might result in a low extraction efficiency due to the chemical similarity of the uranium in the target and actinium produced. However, as the volatility of Ac is higher, one can expect the direct production of an Ac beam.

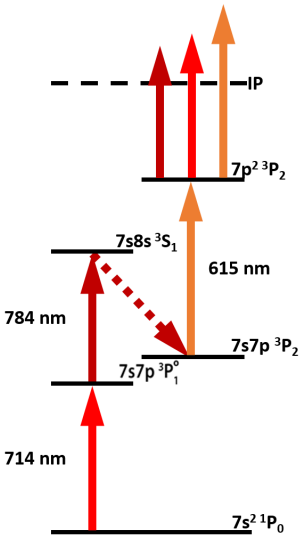

Figure 2: Optimal resonance laser ionization scheme for radium.[15]

The optimized collection of these isotopes is limited by the lack of recent and accurate data for their yield and release curves. For francium, some measurements have been done for the calculation of the release parameters. However, they are not very consistent due to a lack of systematic and elaborate recent data. For radium and actinium, no data were found at all. It has been proven in the above rationale that detailed knowledge of the release curves results in a faster and more efficient measurement of the yield of these isotopes. Therefore, beam time is requested for a proper and systematic measurement of the yield and release curves of Fr and Ra isotopes. The total requested beam time is 6 shifts, to accurately investigate the release curve of francium by measuring the release curves of ^{205,207,220,221,222}Fr. The yields of these isotopes will also be measured together with $^{218,219,223-228}$Fr. Simultaneously, the release curves of ^{214,220,221,222}Ra can be characterized. Furthermore, the yields of $^{219,223-228}$Ra and ^{225}Ac are investigated. Three of these shifts are requested on a fresh target, while the other three at the end of life of the same target. This will allow the investigation of the fluence dependence of the release curves, as it might be expected that some sintering of the target grains due to the high temperatures will result in a decreased release efficiency of the elements. By doing the measurements on the same target, supplementary uncertainties and influences can be avoided.

Summary of requested shifts: We request 6 shifts to do a full characterization of the release curve and yields of $^{205,207,218-228}$Fr and $^{214,219-228}$Ra and basic yield measurements on ^{225}Ac. Optimally, 3 of these shifts are on a fresh target, while the remaining 3 shifts are close to its end of life.

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Appendix

DESCRIPTION OF THE PROPOSED EXPERIMENT

The experimental setup comprises: (*name the fixed-ISOLDE installations, as well as flexible elements of the experiment*)

Part of the	Availability	Design and manufacturing
Tape Station	☒ Existing	☒ To be used without any modification
Windmill	☒ Existing	☒ To be used without any modification ☐ To be modified
	☐ New	☐ Standard equipment supplied by a manufacturer ☐ CERN/collaboration responsible for the design and/or manufacturing

HAZARDS GENERATED BY THE EXPERIMENT (if using fixed installation:) Hazards named in the document relevant for the fixed Tape Station installation.

Additional hazards with respect to the usual use of the devices:

Hazards	**Windmill**
Thermodynamic and fluidic	
Pressure	
Vacuum	
Temperature	
Heat transfer	
Thermal properties of materials	
Cryogenic fluid	
Electrical and electromagnetic	
Electricity	
Static electricity	
Magnetic field	
Batteries	☐
Capacitors	☐
Ionizing radiation	
Target material [material]	
Beam particle type (e, p, ions, etc)	
Beam intensity	
Beam energy	
Cooling liquids	
Gases	

Calibration sources:	☐
• Open source	☒
• Sealed source	☐
• Isotope	^{241}Am
• Activity	50 Bq
Use of activated material:	
• Description	☐
• Dose rate on contact and in 10 cm distance	
• Isotope / Activity	$^{223-224}$**Ra / 1 MBq**
• Isotope / Activity	^{225}**Ra / 1 kBq**
• Isotope / Activity	^{226,228}**Ra / 10-100 Bq**
Non-ionizing radiation	
Laser	
UV light	
Microwaves (300MHz-30 GHz)	
Radiofrequency (1-300 MHz)	
Chemical	
Toxic	
Harmful	
CMR (carcinogens, mutagens and substances toxic to reproduction)	
Corrosive	
Irritant	
Flammable	
Oxidizing	
Explosiveness	
Asphyxiant	
Dangerous for the environment	
Mechanical	
Physical impact or mechanical energy (moving parts)	
Mechanical properties (Sharp, rough, slippery)	
Vibration	
Vehicles and Means of Transport	
Noise	
Frequency	
Intensity	

Physical	
Confined spaces	
High workplaces	
Access to high workplaces	
Obstructions in passageways	
Manual handling	
Poor ergonomics	