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THE USE OF PSI's IP2 BEAM LINE TOWARDS EXOTIC RADIONUCLIDE DEVELOPMENT AND ITS APPLICATION TOWARDS PROOF-OF-PRINCIPLE PRECLINICAL AND CLINICAL STUDIES

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Abstract

Paul Scherrer Institute (PSI) runs a High Intensity Proton Accelerator (HIPA) facility, where a maximum of 100 µA protons is gleaned from high intensity 72 MeV protons from Injector 2, a separated sector cyclotron, into the IP2 target station. These protons irradiate various targets towards the production of exotic radionuclides intended for medical purposes.

Many radiometals in use today are for the diagnosis of disease, with the most popular means of detection being Positron Emission Tomography. These positron emitters are easily produced at low proton energies using medical cyclotrons, however, developments at these facilities are lacking. The fixed 72 MeV proton beam is degraded at IP2 using niobium to provide the desired energy to irradiate targets to produce the likes of ^{44}Sc, ^{43}Sc, ^{64}Cu and ^{165}Er. Once developed, these proofs-of-principle are then put into practice at partner facilities.

Target holders and degraders require development to optimize irradiation conditions and target cooling. Various options are explored, with pros and cons taken into consideration based on calculations and simulations.

INTRODUCTION

Paul Scherrer Institute (PSI), Switzerland's premier research facility, runs a High Intensity Proton Accelerator (HIPA) amenity as part of its Large Facilities, where three accelerators are connected in series to increase proton beam energy. A Cockroft-Walton accelerator accelerates protons at 870 keV to the Injector II separated sector cyclotron, where the protons are accelerated to 72 MeV at an intensity of ~2.5 mA to the Ring cyclotron. The Ring cyclotron accelerates the protons further to 590 MeV, which is then sent down the beam line to various experimental vaults, before the remainder of the beam is collected in a Pb beam dump, which serves as a neutron spallation source for the Swiss Neutron Source (SINQ) [1].

Along the beam line between Injector II and the Ring cyclotron, the Radionuclide Development/production irradiation station (known as IP2) currently gleans ~50 µA protons from Injector 2, by means of a beam splitter, into the IP2 target station (Fig.1). These protons irradiate various targets towards the production of exotic radionuclides intended for medical purposes.

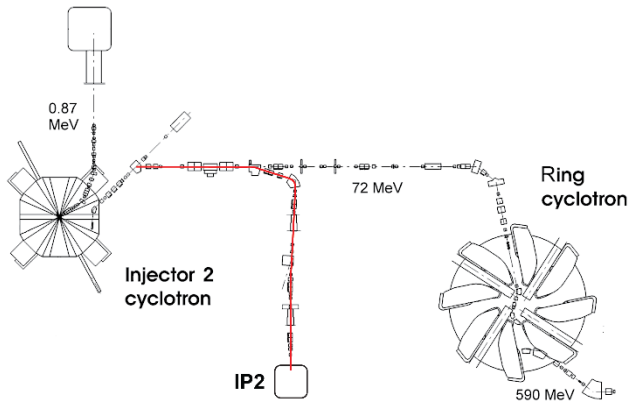

Figure 1: The beam transfer from the Cockroft Walton accelerator via the Injector II cyclotron to the Ring cyclotron. The red line indicates the 72 MeV beam gleaned from Injector II to IP2. Figure adapted from [2].

Many radiometals currently used in nuclear medicine are for the diagnosis of disease, with the most popular means of detection being Positron Emission Tomography (PET). These positron emitters are easily produced at low proton energies using medical cyclotrons, however, development using such facilities are rare.

The irradiation station at IP2 is used for ~9 months of the year and, as a result, cannot be considered for use in any commercial setting. The system is still put to good use, however, towards the development of novel, non-standard radiometals. The station was used to produce the likes of ^{18}F [3] and ^{124}I [4] in a novel way by utilizing its higher beam energy, as well as ^{67}Cu [5], ^{82}Sr and ^{68}Ge, but these activities were halted over a decade ago. As the use of PET increased in popularity for the diagnosis of cancer, the strategy of the station's use was adjusted to meet the growing demand for positron-emitting radionuclides.

Positron-emitting radionuclides are popular, too, because they can easily be produced at medical cyclotrons (with an installed solid target station) utilizing the (p,n) nuclear reaction in the vicinity of 13 MeV protons. To apply this to the revised strategy of IP2's use, it was necessary to degrade from 72 MeV to the desired energy of the radiometal to be produced. Once developed, these proofs-of-principle can then be put into practice at partner facilities.

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BEAM DEGRADATION

The 72 MeV proton beam is degraded at IP2 using niobium (Nb) at various thicknesses to provide the desired energy to irradiate the target in question. The size of degraders range from 1.0 to 3.5 mm and the degradation of the beam (Fig. 2), calculated using SRIM-2013, is listed in Table 1. The values stated are more of an approximation, as this does not take the beam spread, as a result of the degradation of the proton beam, into consideration. Radionuclides developed and produced using this concept include ^{44}Sc [6], ^{43}Sc [7], ^{64}Cu [8] and ^{165}Er [9, 10].

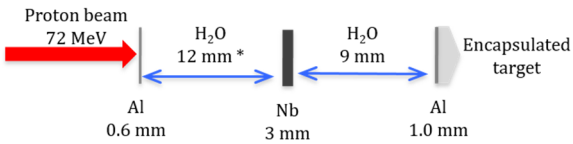

Figure 2: Degrading of the 72 MeV proton beam at the IP2 target station at PSI. The water jacket between the encapsulated target and the degrader remains constant.

Table 1: Nb Degraders used in the 72 MeV Proton Beam at IP2 Irradiation Station at PSI and their Degrading Effect

Nb Degrader Thickness (mm)	Proton Beam Energy on Target (MeV)
1.0	34.1
1.8	28.1
2.0	26.4
2.2	24.7
2.4	22.8
2.8	18.6
3.0	16.2
3.1	14.9
3.2	13.4
3.3	11.8
3.4	10.3
3.5	8.6

The target holders used for the irradiation of targets have not changed much over the years, however, there is place for the fitting of the degrader (Fig. 3). There have been concerns raised with regard to the cooling of the target and initial simulations indicate that there are areas where the water cooling of the target may be optimized (Fig. 4).

Currently, an updated system is being designed such that multiple degraders (maximum of 1 mm thick) are used for the same effect, so that the flow of water through the holder is increased, thereby, improving the cooling of the target. Initial simulations have been performed and, based on the result, a prototype created using a 3D printer (Fig. 5). The prototype was tested in a hot cell, using manipulators, to determine the practicality of installation and removal of the target capsule and degrader stack, respectively.

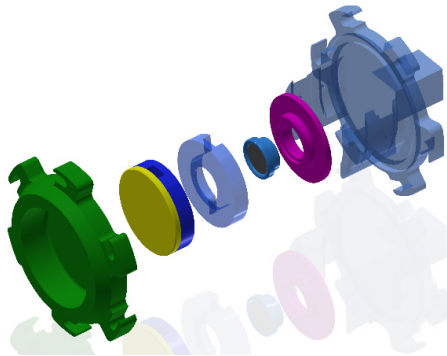

Figure 3: Blown-up layout of target holder containing the target capsule and degrader (blue and yellow).

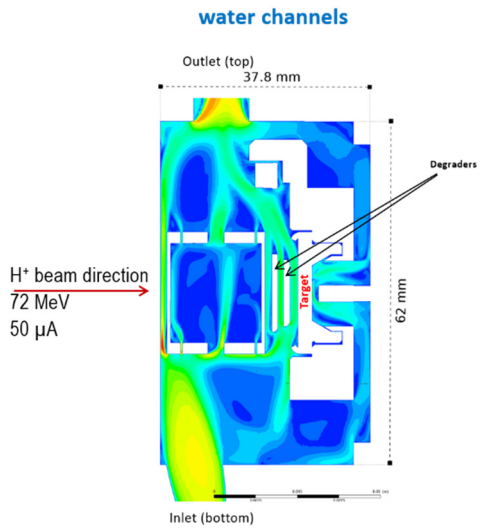

Figure 4: Contour plot of the velocity profile from fluid dynamics simulations through the target holder and degrader in an earlier prototype. Blue indicates a slow velocity ($1x10^{-3}$ m.s^{-1}), green ~1 m.s^{-1}, yellow ~1.5 m.s^{-1} and red the highest velocity at ~ 2 m.s^{-1}.

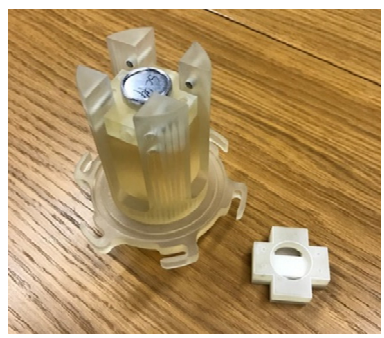

Figure 5: Prototype of target holder, containing a ^{44}Sc target capsule, with a stacked degrader lying next to it.

TARGET PREPARATION

As the (p,n) nuclear reaction is often utilized for irradiation purposes and radionuclidic purity of products for nuclear medicine purposes is vital, one has to turn to the use of enriched target material to obtain the desired nuclear reaction and product. These materials are generally expensive and one has to be able to optimize the targets such that

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enough activity is produced from as little material as possible. Sometimes, the target material cost is such that one has to devise a means of recycling the target material post production.

Enriched oxide targets have been designed to be 6 mm in diameter and 0.5 mm thick (Fig. 6), while the target for ^{64}Cu production consists of an enriched Ni-plated Au foil, 10 mm in diameter [8]. This concept has been slightly adapted for use at the cyclotron facility at the University of Bern, however, the capsule and target design has been used directly towards the design of the solid target station (with an IBA Cyclone 18/9) recently built at ETH Zurich.

Figure 6: Pressed salt target, 6 mm in diameter, nestled in the indentation of an Al (99.5 % pure) capsule.

RADIONUCLIDE DEVELOPMENT AT IP2

^{44}Sc

^{44}Sc is seen as a potentially ideal radiometal for PET, as its half-life ($T_{1/2}$ = 3.97 h) is longer than ^{68}Ga (currently the most popular radiometal in use for PET; $T_{1/2}$ = 68 min) and has better resolution than its Ga counterpart. ^{44}Sc was initially obtained from a ^{44}Ti/^{44}Sc generator, where the parent (^{44}Ti) radionuclide would decay into the daughter (^{44}Sc) and the daughter would be eluted (or "milked") from the generator. The disadvantage of such a system is two-fold: the production rate for producing ^{44}Ti (from Sc) is extremely low, thereby, only producing low-activity generators from which ^{44}Sc can be obtained. Secondly, the half-life of the parent ($T_{1/2}$ = 60 a) is such that breakthrough from the generator could have disastrous consequences in a clinical setting [6].

^{44}Sc can also be produced at a cyclotron via the ^{44}Ca(p,n)^{44}Sc nuclear reaction. Initially, enriched $CaCO_3$ targets were pressed onto graphite and irradiated at ~11 MeV protons at 50 µA beam intensity (currently using a 3.4 mm degrader – Table 1), however, the targets were not homogeneous and 6 mm pressed pure carbonate targets were developed to replace them. It was subsequently discovered that the carbonate targets would easily dissociate in the beam, with the release of radioactive oxygen, and it was decided to further develop the target material. Enriched carbonate targets were converted to oxide targets, which were found to be far more robust under irradiation conditions [11].

Irradiated targets were dissolved in nitric acid and loaded onto a column containing DGA extraction resin, where the ^{44}Sc was retained and the Ca target material passed through the system. This was collected separately and subsequently recycled to make new targets. The desired ^{44}Sc was eluted with dilute hydrochloric acid and concentrated onto a second, smaller, resin column. The final product was eluted in a small volume such that it could be used effectively for preclinical [12] and clinical studies [13].

The system was converted and implemented at the medical cyclotron facility at the University of Bern, which houses an IBA Cyclone 18/18 with a solid target station. The enriched CaO pellet was the same, however, the encapsulation design was customized to fit into the target station [11].

^{43}Sc

While ^{44}Sc is an attractive PET radionuclide, it has the disadvantage of the emission of a γ-ray at 1157 keV, with almost 100 % intensity, having implications on radiation protection and image quality. A suggested alternative is ^{43}Sc, with a similar half-life ($T_{1/2}$ = 3.89 h), but its γ-emission at 373 keV is at 22.5 % intensity, thereby, decreasing dose to the clinical operator and patient and slightly improving image resolution.

^{43}Sc is more difficult to produce than its ^{44}Sc counterpart: production cross sections using the two most popular production routes is lower than for ^{44}Sc [7] and the means to produce it is more expensive, thereby, making it less attractive to introduce into the clinic. It is produced at IP2 via the ^{46}Ti(p,α)^{43}Sc nuclear reaction (using a 3.2 mm Nb degrader – Table 1) or via the ^{43}Ca(p,n)^{43}Sc nuclear reaction using similar irradiation conditions to that of ^{44}Sc production.

The $^{46}Ti_2O_3$ was initially reduced to Ti powder and then pressed into a graphite pellet for irradiation. The beam intensity was reduced to 20 µA for optimum irradiation and target dissolution conditions. The Ti target was dissolved in concentrated hydrochloric acid, diluted slightly and passed through a DGA extraction resin column, where the Sc was retained and the Ti collected for recycling. The Sc was eluted in dilute hydrochloric acid and concentrated on a small SCX cation exchange column. The product was eluted in a small volume of hydrochloric acid/sodium chloride solution. While radionuclidic purity was high (>98 %), the separation was time-consuming and the yields relatively poor [7].

^{43}Sc production and separation from enriched Ca was performed as for ^{44}Sc. Enrichment of ^{43}Ca determines radionuclidic purity of the product, in this case, 57 % enriched ^{43}Ca produced 66.6 % ^{43}Sc and 33.3 % ^{44}Sc. The chemical separation, in comparison to the Ti route, was simple and fast and the yield considerably higher, however the target material is prohibitively expensive.

A more recent approach was taken to make this radionuclide, namely, via the ^{44}Ca(p,2n)^{43}Sc production route [14].

Enriched ^{44}CaO pellets were encapsulated and irradiated as for ^{44}Sc, instead, the Nb degrader used was 2.0 mm thick – coinciding with ~26.4 MeV protons. High yields were

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obtained, with >70 % ^{43}Sc obtained along with co-produced ^{44}Sc. The product was of high chemical purity, confirmed by the ability to use it for high-specific radiolabelling of biomolecules.

^{64}Cu

^{64}Cu is a medically-interesting PET radionuclide with a longer half-life than many of its radiometal counterparts used for similar purposes ($T_{1/2}$ = 12.7 h). It is known to produce images of high resolution. The means of producing it is via the ^{64}Ni(p,n)^{64}Cu nuclear reaction and the target material required to produce this radionuclide is expensive. A thin layer of enriched Ni is electroplated onto 0.5 mm thick gold foils as preparation of targets for irradiation.

The irradiated ^{64}Ni (irradiated with a proton beam degraded with 3.4 mm Nb at 50 µA beam intensity) was dissolved from the gold foil in hydrochloric acid and subsequently diluted to obtain a concentration of 0.1 M hydrochloric acid and 60 % acetone mixture. This resultant solution was passed through a macroporous cation exchange resin column (AG MP-50), where both Cu and Ni were retained. The concentration of acetone was adjusted to elute the ^{64}Cu final product first, while the Ni is finally eluted in hydrochloric acid and collected for recycling purposes [8]. The radionuclide has been used extensively for preclinical studies.

^{165}Er

^{165}Er is a pure Auger-emitting radiolanthanide and is regarded as an interesting option towards targeted radionuclide therapy. It emits no γ-rays and can be detected with its low energy X-rays. It can be produced by means of low-energy protons via the ^{nat}Ho(p,n)^{165}Er nuclear reaction (referred to as the "direct" route) or at higher proton energies via the ^{166}Er(p,2n)^{165}Tm→^{165}Er nuclear reaction (referred to as the "indirect" production route).

The direct route utilized pressed Ho_2O_3 targets 13 mm in diameter, as the 6 mm diameter target produced relatively low activities of product. The beam settings had to be adjusted accordingly, however, the beam intensity had to be reduced to 20 µA, as any higher intensity had a negative impact on the production yield. The same irradiation parameters were applied to the indirect production route, however, a 6 mm target was prepared for the irradiation of enriched target material (Fig. 6) [9, 10].

An adapted chemical separation method, based on that determined for ^{161}Tb production at PSI [15] was adopted.

CONCLUSIONS AND OUTLOOK

The IP2 target station at PSI has proven to be an effective tool towards proof-of-principle development of exotic radionuclides in Switzerland. Its effectiveness has resulted in small, long overdue upgrades planned to improve irradiation conditions. A new target holder has been designed and is under construction, with initial tests planned within the next year. Other upgrades, such as beam position diagnostics, are envisaged in the near future.

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