NOVEL IRRADIATION METHODS FOR THERANOSTIC RADIOISOTOPE PRODUCTION WITH SOLID TARGETS AT THE BERN MEDICAL CYCLOTRON*

S. Braccini[1,†], C. Belver Aguilar[1], T. S. Carzaniga[1], G. Dellepiane[1], P. D. Häffner[1], P. Scampoli[1,2]
[1] Albert Einstein Center for Fundamental Physics (AEC), Laboratory for High Energy Physics (LHEP),
University of Bern, Sidlerstrasse 5, 3012 Bern, Switzerland
[2] Department of Physics “Ettore Pancini”, University of Napoli Federico II,
Complesso Universitario di Monte S. Angelo, 80126 Napoli, Italy

Abstract

The production of medical radioisotopes for theranostics is essential for the development of personalized nuclear medicine. Among them, radiometals can be used to label proteins and peptides and their supply in quantity and quality for clinical applications represents a challenge. A research program is ongoing at the Bern medical cyclotron, where a solid target station with a pneumatic delivery system is in operation. To bombard isotope-enriched materials in form of compressed powders, a specific target coin was realized. To assess the activity at EoB, a system based on a CZT detector was developed. For an optimized production yield with the required radio nuclide purity, precise knowledge of the cross-sections and of the beam energy is crucial. Specific methods were developed to assess these quantities. To further enhance the capabilities of solid target stations at medical cyclotrons, a novel irradiation system based on an ultra-compact ~50 cm long beam line and a two-dimensional beam monitoring detector is under development to bombard targets down to few mg and few mm diameter. The first results on the production of ^{68}Ga, ^{64}Cu, ^{43}Sc, ^{44}Sc and ^{47}Sc are presented.

INTRODUCTION

The availability of novel medical radioisotopes is a key issue for advances in nuclear medicine. Of particular interest are the so-called theranostic pairs, which consist of one radionuclide used for diagnostics (β^+ or γ emitter for PET or SPECT) and one for therapy (β^-, Auger or α emitter for radio-immunotherapy). The two radionuclides must have very similar or identical chemical properties, as in the case of isotopes of the same element. They can be used to label the same biomolecules that, once injected into the patient’s body, undergo the same metabolic processes. In this way, they allow treating the disease and, at the same time, assessing their uptake and following the evolution of the therapy by means of medical imaging. Along this line, radiometals can be bound to proteins and peptides and a few of their isotopes form the most promising pairs , such as ^{43,44}Sc/^{47}Sc and ^{61,64}Cu/^{67}Cu.

The availability of these radionuclides represents the bottle-neck for the development of theranostics in nuclear medicine. To solve this problem, the large number (> 1000 worldwide) of compact medical cyclotrons [1] could be exploited to produce the diagnostic partner of the pair and, in some cases, also the therapeutic one. Being designed to produce ^{18}F, which is presently the main PET radioisotope, medical cyclotrons provide proton beams of low energy (about 20 MeV) and relatively high intensity (>100 µA). For the production of radiometals, very rare and expensive isotope enriched materials have to be bombarded. They are often available in form of powder and, to obtain high yields, the use of a solid target station represents the best solution. Solid target stations for compact medical cyclotrons are rare. They are designed to irradiate target coins on which the enriched material is electroplated, a methodology that is not suitable for the production of several radiometals. For the bombardment of compressed materials in form of powder and to irradiate solid targets of small dimensions (about 6 mm diameter or less) novel irradiation instruments and methods have to be conceived and developed.

We report here about some of the developments and results obtained in the framework of the research programs ongoing at the cyclotron laboratory in operation at the Bern University Hospital [2, 3]. This facility is based on an IBA Cyclone 18/18 medical cyclotron (18 MeV proton beams, max. 150 µA extracted current, 8 out ports), which is used for routine production of ^{18}F during the night and for multidisciplinary research activities during the day. For the last purpose, it is equipped with a 6 m long Beam Transport Line (BTL) bringing the proton beam to a second bunker with independent access. Although uncommon for a hospital-based facility, this solution was fundamental to obtain the results reported in this paper.

SOLID TARGET DEVELOPMENTS AND FIRST RESULTS

To pursue our research program on novel medical radioisotopes, an IBA Nirta Solid target station was installed in one of the out ports of the cyclotron together with a pneumatic solid target transfer system (STTS) by TEMA Sinergie. The STTS was customised in such a way that the shuttle containing the irradiated target can be sent either to one hot cell in the nearby GMP radio-pharmacy or to a receiving

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† saverio.braccini@lhep.unibe.ch

station located in the BTL bunker. The latter option is used for all non GMP activities and when the irradiated target is transported to external research laboratories for separation and labelling.

The solid target station was designed to bombard a disk (24 mm diameter, 2 mm thick) on which the target material is electroplated, as in the case of ^{64}Cu production via the reaction ^{64}Ni(p,n)^{64}Cu. This method is not suitable to produce scandium isotopes that can be obtained by irradiating powders compressed in pellets made of $CaCO_3$ or CaO. For this purpose, a specific magnetic "coin" target disk was conceived and constructed. As shown in Fig. 1, the coin has the same external dimensions as an ordinary disk but is composed of two halves kept together by small permanent magnets. The choice of its components and its manufacturing is challenging. In particular, the magnets should not loose their properties due to the high temperatures (>200 °C) that are reached during irradiation, although the disk is cooled by water on the back and by helium on the front side. The coin is constructed using an aluminum alloy (EN AW-6082) while other materials characterised by high melting point and low residual activation (such as niobium) are considered. The front window of the coin is used to adjust the energy of the protons reaching the target material. Due to the high cost of enriched materials, 30 mg of CaO were used for the case of ^{44}Sc, giving a 6 mm diameter and 500 µm thick pellet. It is important to remark that a very good thermal contact between the two halves of the magnetic coin and the target material is mandatory to assure good cooling, thus avoiding target and coin melting.

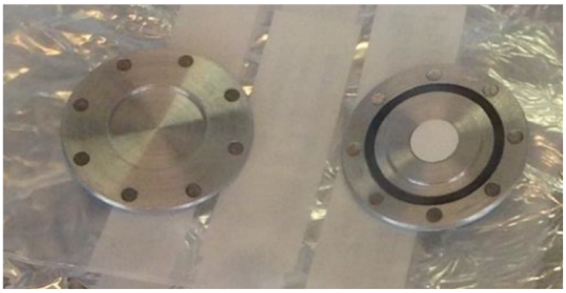

Figure 1: The two halves of the "coin" target. The front part (on the left) is used to degrade the beam to the desired energy. The rear half (on the right) contains the 6 mm diameter pellet and hosts an o-ring to assure gas tightness.

Being the beam extracted from the cyclotron ~12 mm FWHM at the solid target station in standard irradiation conditions, only about 25% of the extracted protons are effectively used to produce the desired isotope if a 6 mm pellet is used. This fact produces unwanted residual activity in the coin with consequent radiation protection and transport limitations. Furthermore, overheat is produced during the irradiation with limitations on the total beam current. To improve this issue, a novel irradiation system described later in this paper is under development. It has to be remarked that some powder materials are available in form of oxide and the reaction ^{16}O(p,α)^{13}N produces a relevant amount of activity in gas form provoking radiation protection issues. For this reason, an o-ring was embedded in the coin to contain the radioactive gas (Fig. 1). For the case of scandium, this is particularly critical if $CaCO_3$ is used due the increase of pressure caused by the production of CO_2 by dissociation. For this reason, a method for the production of CaO targets was developed [4].

The produced activity and the radionuclidic purity can be optimised on the basis of an accurate knowledge of the reaction cross-sections by choosing the appropriate thicknesses of the cyclotron exit window, of the front part of the coin and of the pellet. Several versions of the magnetic coin target were therefore realised for each specific radionuclide to be produced. In particular, a coin was made to irradiate thin foils at the maximum possible beam energy featuring a front part made of a ring without any absorber in front of the target material. On the basis of the cross sections and by measuring the current on target during irradiation, the produced activity can be estimated. To experimentally assess the produced activity after EoB and the delivery of the shuttle, a CZT detector system was designed and installed about 1 m away from the receiving station. Based on a ~1 cm^3 CdZnTe crystal (GBS Elektronik), this detector allows recoding the energy spectra of the gamma rays emitted by the target (coin and pellet). The low detection efficiency due to the distance and the small volume of the crystal is well suited for the high produced activities. Once calibrated by means of an HPGe detector, the signal of the CZT allows measuring the produced activity with an accuracy of a few per cent [5].

Thanks to these developments, several radionuclides have been produced during the first two years of operation of the solid target station, as reported in Table 1. In particular, the production of about 15 GBq of ^{44}Sc represents a promising

Table 1: Main Achievements in Non-Standard Radioisotope Production Obtained During the First Two Years of Operation of the Solid Target Station at the Bern Cyclotron. The Beam Current Corresponds to the Protons Hitting the Target Material.

Isotope	Reaction	Target Material	Beam Current [µA]	Irradiation Time [h]	A_{EOB} [GBq]
^{44}Sc	(p,n)	Enriched CaO pellet	5	5	~15
^{64}Cu	(p,n)	Enriched Ni deposition	15	10	~20
^{68}Ga	(p,n)	Enriched Zn pellet	5	0.5	~15
^{48}V	(p,n)	Ti metal foils	10	1	~0.15
^{65}Er	(p,n)	Ho metal disk	10	10	~1.5

result in view of theranostic clinical applications. Production tests of ^{43}Sc and of the therapeutic partner ^{47}Sc are foreseen in the near future using the same methodology. In particular, we expect to obtain about 10 GBq of ^{47}Sc, an adequate quantity for clinical trials. The results we obtained on the production of ^{68}Ga [5] are at the basis of on-going developments aimed at improving the scarce supply of this radionuclide by Ge/Ga generators. Developments in fundamental physics were also pursued. ${}^{143-147}$Pm radioisotopes from a Nd oxide target were produced in enough quantities to be studied by high-precision laser spectroscopy. The production of very thin ^{48}V positron sources may open new avenues to obtain positron beams for fundamental and applied research using a table-top apparatus [6].

BEAM CHARACTERIZATION

To enhance the production capabilities of compact medical cyclotrons in the production of unconventional radioisotopes, an accurate knowledge of the beam characteristics is mandatory in order to be able to effectively bombard small targets (6 mm diameter or less) and to reduce to a minimum the irradiation of other materials.

Beam Monitoring Detectors

Beam monitoring detectors are essential in accelerator facilities and our group is engaged in developing specific devices to complement the standard equipment (destructive beam viewers) provided by the manufacturer of the cyclotron and the BTL.

A high sensitivity Faraday cup was developed [7] to measure beam currents down to the pA range.

The UniBEaM detector [8] is an optical wire scanner that consists of a 200 µm diameter 10 cm long doped silica fibre passed through the beam. The collected light allows measuring the beam profile in an almost non-destructive way with a precision of about 0.1 mm. This instrument can detect beams in a wide range of intensities (from 1 pA to about 10 µA) and, being linear up to about 1 µA, can be used to assess the total beam current by integrating the beam profile. This device is commercialised by the Canadian company D-Pace [9] and can provide profiles in two orthogonal axes by using two fibres moved in orthogonal directions.

The π^2 detector is based on the collection by a CCD camera of the light produced by the beam on a few µm thick P47 phosphor screen deposited on a 1 µm aluminum foil (Fig. 2). The foil can be removed from the beam path via a pneumatic mechanism. This device allows measuring a two-dimensional beam profile in an almost non destructive way.

Transverse Beam Emittance

The transverse beam emittance was first assessed using the BTL by means of the standard and time consuming quadrupole variation method. Based on four UniBEaM detectors located at a distance of about 50 cm one another along the beam path, a novel system (dubbed ^{4}PrOBεaM) capable of measuring the transverse beam emittance quasi on-line was realised [10]. Based on the acquisition of four consecutive beam profiles, the transverse beam emittance can be measured in less than one minute. This system allowed to study the transverse beam emittance as a function of several parameters such as the current in the main coil of the cyclotron or the radio-frequency peak voltage.

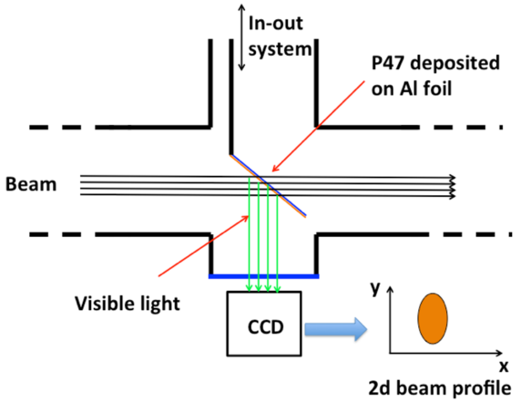

Figure 2: Scheme of the π^2 beam-monitoring detector. The intensity of the light emitted by the P47 coating is proportional to the intensity of the beam and is recorded by a CCD camera.

Beam Energy

The beam energy of the pristine proton beam is an essential parameter for an optimised radioisotope production with solid targets. We measured the beam energy with different methods based on the assessment of the beam current after passive absorbers of different thickness [10], on a multi-leaf Faraday cup [11] and on Rutherford Back Scattering (RBS) [12]. A further apparatus based on the deflection of the beam by a dipole electromagnet and on the measurement of the beam position by a UniBEaM detector was conceived and realised to assess the beam energy as a function of cyclotron operational parameters as the current in the main coil. The beam energy extracted on the BTL was measured to be (18.3 ± 0.3) MeV in resonance conditions, a slightly higher value with respect to the nominal value of 18 MeV due to the modified position of the stripper foil [3].

CROSS SECTION MEASUREMENTS

A novel method to measure cross-sections with a medical cyclotron was developed [13]. It relies on the irradiation of a known mass with a flat beam current surface density instead of the usual method based on the irradiation of a homogeneously thick target. The beam is flattened by means of the optical elements of the BTL and monitored on-line by means of the UniBEaM and the π^2 detectors. Before hitting the target, protons cross thin aluminum discs used to degrade their energy that was calculated on the basis of our measurement of the pristine beam energy and by Monte Carlo simulations (SRIM). The integrated charge due to the protons passing through the collimator is recorded and the obtained activity measured by HPGe gamma spectroscopy. With this method, the production cross section of several radioisotopes (^{43}Sc, ^{44}Sc [13, 14], ^{48}V [13], ^{68}Ga [5] and ^{44m}Sc, ^{47}Sc, ^{48}Sc, ^{47}Ca [15]) was measured.

FUTURE DEVELOPMENTS

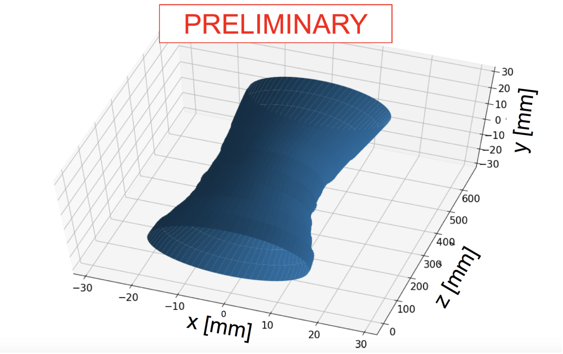

Figure 3: Three dimensional reconstruction of the beam envelope based on the measurements by the π^3 detector.

To enhance and optimise the production capabilities of solid target stations at compact medical cyclotrons, a novel irradiation system able to focus the beam down to the diameter of the pellet (~6 mm or less) and to keep it always on target is under development. With this system, we expect to enhance the production activity at EoB of a factor five for the same extracted current of 20 µA for the case of ^{44}Sc. Since basically all the hospital-based cyclotron facilities do not dispose of a long beam line, this apparatus must be very compact (about 1 m long) to be installed in the same bunker as the accelerator. This apparatus is composed of a compact 50 cm long Mini-Beam-Line (MBL) and a two-dimensional beam monitoring detector (dual axis UniBEaM or π^2) located just in front of the solid target station. The MBL is produced by the company D-Pace [16] and consists of a quadrupole doublet with embedded two (one vertical and one horizonal) steering dipoles. A software feedback system collects and analyses the data from the detector and, if necessary, acts on the power supplies of the MBL to correct the beam position and shape. For this purpose, an accurate characterisation of the MBL is necessary and beam tests are on-going by means of the BTL. Simulations of the beam optics with the MAD-X software are performed. Due to the compactness of the optical elements of the MBL, beam optics has to be studied carefully. For this purpose an innovative three dimensional beam monitoring detector has been conceived and built, dubbed π^3. This detector consist of a small foil like the π^2 and a small camera connected to it that operates under vacuum. The screen and the camera are moved inside the beam pipe and images of the beam are acquired at distances of 1 mm inside the magnetic elements of the MBL. Focusing, defocusing and steering effects can be directly measured and a full three-dimensional reconstruction of the beam obtained [17]. A first preliminary reconstruction of the beam envelope is shown in Fig. 3.

CONCLUSIONS AND OUTLOOK

A research program aimed at the production of non-conventional radioisotopes is on-going at the Bern cyclotron laboratory. Novel irradiation instruments and methods were conceived, realized and tested based on accelerator and detector physics developments. The promising results obtained represent a valuable step towards the establishment of efficient and reliable radioisotope supply using compact medical cyclotrons in view of theranostic applications in nuclear medicine.

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