https://doi.org/10.1051/epjconf/202328509003

Novel solid target and irradiation methods for theranostic radioisotope production at the Bern medical cyclotron

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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 suitable for clinical applications represents a scientific challenge. A research program is ongoing at the Bern medical cyclotron, where an IBA Cyclone 18/18 HC is in operation. The cyclotron provides 18 MeV proton beams up to 150 μA and is equipped with a Solid Target Station (STS) and a 6 m Beam Transport Line (BTL), ending in a separate bunker with independent access. A novel magnetic target coin was realized to bombard isotope-enriched materials in the form of compressed powders, together with a compact focalization system to enhance the irradiation procedure. For an optimized production yield with the required radionuclidic purity, novel methods were developed to precisely measure the extracted beam energy and the involved reaction cross sections. In particular, a target station was realized to measure nuclear cross sections using materials in the form of powder deposited on an aluminium disc by sedimentation, bombarded by a monitored flat beam.

1 Introduction

The availability of novel radionuclides is of paramount importance for the development of personalised nuclear medicine. For the theranostic approach, a pair of radionuclides with identical or very similar chemical properties is required to label the same biomolecule, combining diagnostic imaging and therapy. A diagnostic radionuclide (β^+- or γ- emitter) is used to detect possible diseases and to monitor the dose deposition imparted by means of the therapeutic radionuclide (β^--, Auger- or α- emitter), allowing to predict whether the patient will benefit from the treatment. For theranostics to be established in the clinical setting, a stable and sustainable supply of radionuclides in quantity and quality suitable for medical applications is required. The use of small medical cyclotrons and solid targets represents a promising solution. In this case, however, the precise knowledge of the beam characteristics during the irradiation is of paramount importance, and new instruments and methods are required. In this paper, we report about some of the developments and results obtained in the framework of a research program on-going at the Bern University Hospital (Inselspital) cyclotron laboratory [1]. This research is aimed at optimising novel radionuclide production with solid targets. The facility hosts an IBA Cyclone 18/18 HC medical cyclotron (18 MeV proton beams, maximum current of 150 μA), equipped with 6 liquid targets for routine ^{18}F production, an IBA Nirta Solid Target Station (STS) and a 6 m long Beam Transport Line (BTL) that brings the beam in a second bunker with independent access to the experimental area. This solution allows multidisciplinary research activities [2-4] to be carried out in parallel with the industrial production of ^{18}F-labelled PET radiotracers.

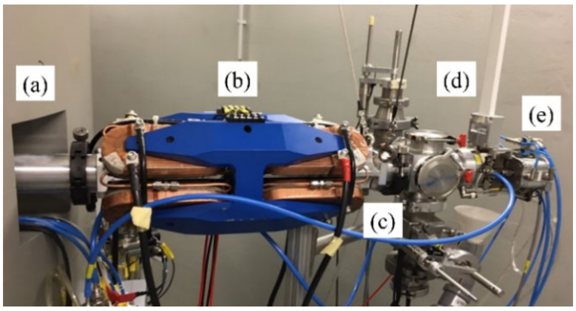

Fig. 1. The STS installed in the out-port of the cyclotron through the AFS: (a) cyclotron out-port; (b) Mini-PET beam line; (c) UniBEaM detector; (d) target receiving station of the hyperloop; (e) Solid Target Station.

2 Solid target developments

The STS is installed in one out-port of the cyclotron and allows to produce novel radioisotopes from materials in solid form. As shown in Fig. 1, the STS is connected to the cyclotron through the Automatic Focusing System (AFS), conceived by our group to enhance the

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*Corresponding author: gaia.dellepiane@lhep.unibe.ch irradiation performance [5]. The AFS is composed of the Mini-PET Beamline (MBL) [6], a two-dimensional beam profiler (UniBEaM [7]) and a software feedback system. The MBL is an innovative compact (50 cm long) pipe produced by the Canadian company D-Pace, embedding two quadrupoles and two steering magnets. The UniBEaM detector is a non-destructive two-dimensional beam profiler based on scintillating silica doped fibers passing through the beam. This detector was developed by our group and was successfully tested with a continuous 18 MeV proton beam in the current range from 1 pA to 20 μA [8]. A commercial version of the UniBEaM, shown in Fig. 2, is manufactured by D-Pace [9].

Fig. 2. Commercial version of the UniBEaM detector, produced by D-Pace.

The AFS steers and focuses the beam on target, controls its size and position and corrects its characteristics by means of the iterative feedback algorithm. This system allows to hit the target with the full beam extracted from the cyclotron, limiting overheating during the irradiation and unwanted residual activity, which would give rise to radiation protection issues.

During the irradiation, the target is contained in a special magnetic capsule, developed by our group to irradiate materials in the form of pressed powder pellets or solid foils. This capsule, called "coin" and shown in Fig. 3, is composed of two aluminium or niobium halves kept together by small permanent magnets. The thickness of the front part is used to adjust the energy of protons reaching the target material, in order to optimise the produced activity and the radionuclidic purity. The back part hosts the 6-mm-diameter target and an O-ring to prevent the leakage of any molten material or gas produced during the irradiation.

Fig. 3. The front and the back parts of the coin target (24 mm diameter, 2 mm thick).

The depth of the pocket containing the target can be varied from a few tens of μm (e.g. for irradiating materials in the form of thin foils) to about 1 mm.

To avoid overheating during the irradiation, the coin is water-cooled and helium-cooled, on the back and front sides, respectively. The body of the STS is connected to a B29885A Keysight electrometer to measure the current on-line during the irradiation. Radiochromic films [10] are used to measure the 2D beam profiles and allow to assess the effective current hitting the 6-mm pellet with an uncertainty within 10%.

Specific systems were implemented to load and unload the station without entering the cyclotron bunker, minimising the dose to personnel [11]. The target is inserted in the STS by means of a mechanical transfer system, called Hyperloop and shown in Fig.4-a, developed by our group. After the irradiation, it is transferred from the bunker area by means of the Solid Target Transfer System (STTS) by TEMA Sinergie (Fig. 4-b). The target can be delivered either to one hot cell in the nearby GMP radio-pharmacy, where the chemical processes are performed, or to a receiving station located in the BTL bunker (Fig. 5-a) for further analysis or for transport to external research laboratories. To assess the produced activity, the receiving station was equipped with a CZT detector system based on a ~1 cm^3 CdZnTe crystal (GBS Elektronik), shown in Fig. 5-b. The low counting efficiency makes this detector suitable for the high activities produced; moreover, its position can be modified by means of a programmable step monitor, up to a maximum of about 50 cm from the source. The CZT was experimentally calibrated with a High Purity Germanium (HPGe) detector, considering that the target always has the same size and lands with the same orientation. The system allows measuring the produced activity with an accuracy of a few percent [12]. Thanks to these developments, several radionuclides have been produced at the Bern medical cyclotron with solid targets, as reported in Table 1 [13]. In particular, the production of about 15 GBq of ^{44}Sc represents a very promising result in view of theranostic clinical applications [14].

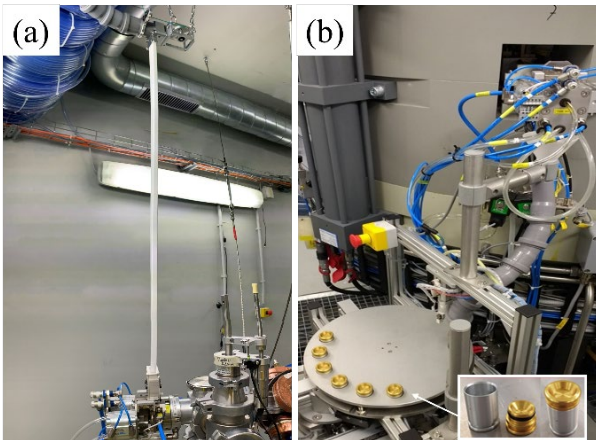

Fig. 4. (a) The Hyperloop connected to the STS; (b) the IBA Nirta STS and the STTS by TEMA Sinergie installed on the Bern medical cyclotron.

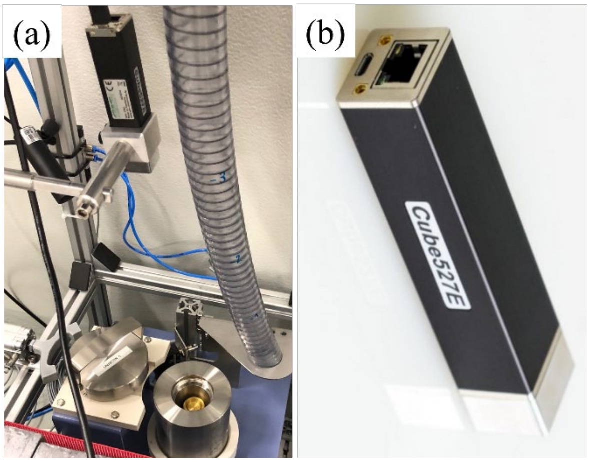

Fig. 5. (a) The receiving station located in the BTL bunker; (b) the CZT detector from GBS Elektronik.

Table 1. Main achievements in non-standard radioisotope production obtained with the STS at the Bern medical cyclotron.

Isotope	Reaction	Target	Mass [mg]	Y [GBq/μAh]
^{44}Sc	(p,n) (p,α)	enr. ^{44}CaO enr. ^{47}TiO$_2$	30 65	0.6 0.05
^{47}Sc	(p,α)	enr. ^{50}TiO$_2$	35	0.001
^{61}Cu	(p,α)	enr. ^{64}Zn	40	0.14
^{64}Cu	(p,n) (p,α)	enr. ^{64}Ni enr. ^{67}ZnO	63 59	0.13 0.02
^{67}Cu	(p,α)	enr. ^{70}ZnO	34	0.001
^{68}Ga	(p,n)	enr. ^{68}Zn	40	4.5
^{155}Tb	(p,n) (p,2n)	enr. ^{155}Gd$_2$O$_3$ enr. ^{156}Gd$_2$O$_3$	40 40	0.004 0.01
^{165}Er	(p,n)	nat. Ho	160	0.07
^{165}Tm	(p,2n)	enr. ^{166}Er$_2$O$_3$	59	0.02
^{167}Tm	(p,n) (p,2n)	enr. ^{167}Er$_2$O$_3$ enr. ^{168}Er$_2$O$_3$	41 40	0.003 0.009

3 Beam energy measurements

The accurate knowledge of the proton beam energy is of paramount importance for an optimised production of novel radioisotopes for medical applications, where high radionuclidic purities are required.

In the out-port of the BTL, the extracted beam energy was accurately measured with different methods [15-17]. In particular, an apparatus based on the beam deflection by a dipole electromagnet allowed to study the beam energy as a function of several operational parameters of the cyclotron and provided a mean energy of (18.59 ± 0.14) MeV for a stripper angle of 97.1° [18]. Inside the cyclotron bunker, however, lack of space prevents the installation of experimental apparatus dedicated to the direct measurement of the beam energy. For this reason, the energy of the beam extracted to the STS out-port was assessed by means of a method based on the stacked-foils technique. The well-known monitor reaction ^{nat}Ti(p,x)^{48}V was chosen for this purpose, being characterised by a particular shape so that the produced activity strongly depends on the beam energy. Stacks of thin titanium layers, separated by 125-μm-thick niobium energy degraders were inserted in the coin pocket and irradiated. A specially designed coin with a hole in the front part was used to prevent the beam from degrading its energy. Each foil was then measured by gamma spectrometry with the HPGe detector, to precisely assess the produced activity. The measured activities were then plotted as a function of the Ti foil's number for several initial energies and an iterative least-squares minimisation method was applied to identify the initial energy that best reproduces the experimental data. The procedure was validated in the BTL and the beam energy measurement in the STS is currently in progress for different stripper angles. This methodology was developed by our group and can be easily applied to any medical cyclotron equipped with a solid target station, without the need of a beam transport line.

4 Cross-section measurements

To maximise the production yield of the desired radionuclide while minimising the production of any radioisotopic impurity, the precise knowledge of the cross sections of the involved nuclear reactions is of paramount importance.

A novel method was developed by our group to measure the cross sections using targets in the form of powder [19]. In most cases, the powder is deposited on an aluminium disc by sedimentation, which means that the target thickness cannot be precisely controlled. For this reason, the new procedure is based on the irradiation of the full target mass with flat proton beams, instead of the usual method based on the irradiation of a homogeneously thick target. The beam is flattened by the optical elements of the BTL and its position and shape are measured on-line with the UniBEaM detector. The beam current hitting the target is measured by means of a custom target station, shown in Fig. 6, composed of a 8 mm diameter collimator, an electron suppressor ring and a target holder. The collimator is grounded and provides a beam of controlled diameter, within which the beam flatness is achieved with an uncertainty within 5%.

The electron suppressor ring is connected to a negative bias voltage in order to repel secondary electrons produced during the irradiation, that would increase the measured beam current. Current measurements are performed on-line during the irradiation connecting the target holder to an ammeter (B29885A Keysight). The conductive parts of the target stations are kept together by insulator components. The beam is degraded by means of aluminium attenuator discs placed in front of the target and is determined using the SRIM Monte Carlo code [20]. The produced activity is assessed by gamma spectrometry with the HPGe detector.

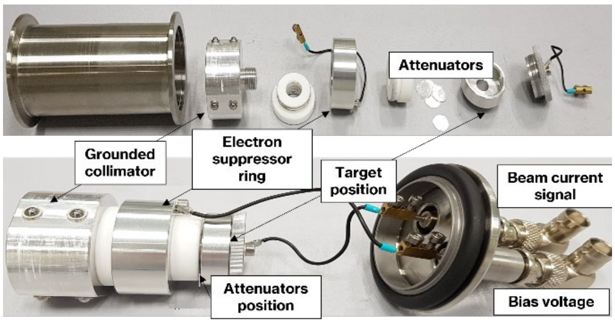

Fig. 6 Target station used for cross-section measurements.

Targets used for cross-section measurements consist of an aluminium 23 mm disc with a 4 mm diameter and 0.8 mm deep pocket in its centre. The target material is deposited by sedimentation method from a suspension of a few milligrams of material in ultra-pure water or ethanol, which is then evaporated. The target mass is assessed with an analytical balance (Mettler Toledo AX26 Delta Range). To prevent possible leakage of the material during the irradiation and the measurement procedure, the disc is covered by a 13 μm thick aluminium foil. With this procedure, target thicknesses of a few tens of μm can be achieved, and the beam energy can be considered constant within the uncertainties over the full irradiated mass. When the radionuclide production is the result of two or more nuclear processes, it is necessary to decouple their contribution to the production cross section. For this purpose, a method based on the inversion of a linear system of equation was developed [21]. It requires measuring the total cross section from as many materials with different isotopic compositions as there are reactions involved in the radionuclide production. With this method, the cross section of the nuclear reactions involved in the production of several radioisotopes (^{43}Sc [19], ^{44}Sc [19], ^{47}Sc [22, 23], ^{48}V [19], ^{61}Cu [24], ^{64}Cu [25], ^{67}Cu, ^{67}Ga [21], ^{68}Ga [21], ^{155}Tb [26], ^{165}Er [27], ^{165}Tm, ^{167}Tm and related impurities) were measured.

5 Conclusions and outlook

In the framework of the research program on the production of novel radioisotopes for nuclear medicine ongoing at the Bern medical cyclotron, new instruments and methods were developed. The irradiation procedure of solid targets was enhanced by developing a new target coin and a novel automatic focusing system. New procedures to measure the nuclear cross sections, the beam energy and the produced activity at EoB were also developed. The promising results obtained so far represent a valuable step toward the use of small medical cyclotrons for an efficient and reliable radioisotope supply in view of theranostic applications in nuclear medicine.

We acknowledge contributions from LHEP engineering and technical staff and from SWAN Isotopen AG team. This research was partially funded by the Swiss National Science Foundation (SNSF). Grants: 200021_175749 and CRSII5_180352.

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