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New developments for theranostic radioisotope production with solid targets at the Bern medical cyclotron

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Abstract. The concept of theranostics in nuclear medicine is based on the use of a pair of radioisotopes to label radiopharmaceuticals for both diagnosis and therapy and is essential for nuclear medicine developments. The production of novel medical radioisotopes using solid target stations is challenging and new instruments and methods are needed. A research program is ongoing at the 18 MeV Bern medical cyclotron, equipped with a Solid Target Station and a 6.5 m Beam Transfer Line ending in a separate bunker. To irradiate isotope-enriched materials in form of compressed powder pellets, a novel target coin was conceived and realized together with methods to assess the beam energy and the production cross sections. To optimize the irradiation procedure, a novel ultra-compact active irradiation system based on a specific magnetic lens and a two-dimensional beam detector was conceived, constructed and tested. The system allows to control on-line the size and position of the beam and to correct its characteristics by steering and focusing it in order to keep it on target. The first results on the production of several radionuclides (^{43}Sc, ^{44}Sc, ^{47}Sc, ^{61}Cu, ^{64}Cu, ^{67}Cu, ^{68}Ga, ^{165}Er, ^{165}Tm, ^{167}Tm and ^{155}Tb) are presented.

1. Introduction

Theranostics is an emerging field of nuclear medicine that involves the use of radionuclides coupled to molecules of biomedical interest for both diagnostic and therapeutic purposes. If the therapeutic radionuclide (α, β^- or Auger emitter) is of the same element as the diagnostic one (β^+ or γ emitter), they have identical kinetics and chemical reactivity and undergo the same metabolic processes. This allows to predict whether a patient will benefit from a therapeutic treatment on the basis of nuclear imaging data, opening the door to the concept of personalised nuclear medicine. The availability of new radionuclides with optimal physical and chemical characteristics is therefore essential for the establishment of theranostics. A stable and sustainable supply of radionuclides in quantities and qualities suitable for medical applications represents a major effort and remains a scientific challenge.

Within this framework, a research program is ongoing at the Bern University Hospital (Inselspital) cyclotron laboratory [1], aimed at optimising novel radionuclide production with solid targets by developing new instruments and methods. In particular, new beam monitors were

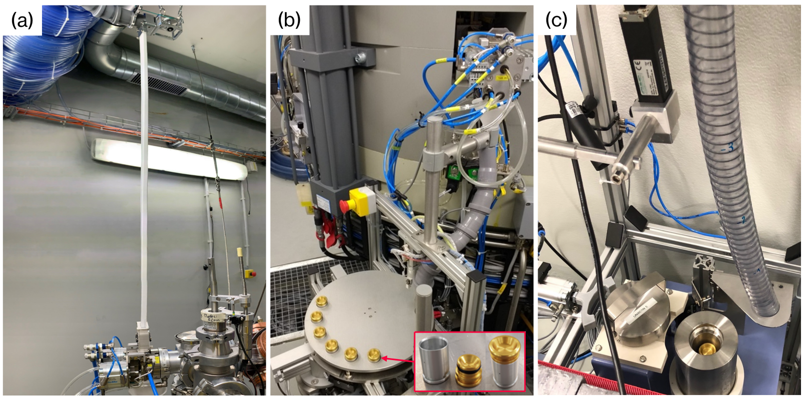

Figure 1. (a) The Hyperloop connected to the STS. (b) The IBA Nirta solid target station and the solid target transfer system by TEMA Sinergie installed on the Bern medical cyclotron. (c) The receiving station located in the BTL bunker.

Figure 2. The front and the back part of the coin target (24 mm diameter, 2 mm thick).

developed, together with a compact automatic focalization system to enhance the irradiation procedure and new techniques for measuring the beam energy and the production cross sections. The facility hosts an IBA Cyclone 18/18 HC medical cyclotron (18 MeV proton beams, beam currents from a few pA to 150 μA, 8 out-ports), equipped with an IBA Nirta Solid Target Station (STS) and a 6.5 m long external Beam Transfer Line (BTL) [2]. The BTL transports the beam to a second bunker with independent access, enabling both routine industrial production of ^{18}F-labelled radiopharmaceuticals overnight and multidisciplinary research activities during the day.

2. Solid target developments and first results

The STS is installed in an out-port of the cyclotron together with automatic systems for loading and unloading the station, minimising the dose to personnel. The target to be irradiated is placed in a loading station shuttle located outside the cyclotron bunker and guided over the STS by means of a cable. It then falls into a narrow conduit that doesn't allow for its rotation, and eventually is locked into the irradiation position. This system, named Hyperloop [3] (Figure 1-a) and developed by our group, is only based on mechanical components and is thus radiation hard. After the irradiation, the target is transferred by means of the Solid Target Transfer System (STTS) by TEMA Sinergie (Figure 1-b). The STTS consists of a shuttle that is brought under the irradiation unit by a rotating plate and opened with an automatic manipulator. The irradiated target falls into the shuttle through a tube connected to the STS body and can be sent either to a hot cell in the nearby GMP radio-pharmacy or to a receiving station located in the BTL bunker (Figure 1-c). The latter option is used when the target has to be transported to external research laboratories for chemical processing or transferred to the physics laboratory of the facility for further analysis. To assess the produced activity, the receiving station was equipped with a CZT detector system based on a $\sim$1 cm^3 CdZnTe crystal (GBS Elektronik). 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 motor up to about 50 cm from the source. The CZT was calibrated by means of a High Purity Germanium detector (HPGe) and allows to assess the End of Beam (EoB) activity with an accuracy of a few percent [4].
The STS was designed to irradiate a gold or platinum disk (24 mm in diameter, 2 mm thick) on which the target material is electroplated. To limit overheating during irradiation, the disk is water-cooled and helium-cooled on the back and front side, respectively. To irradiate materials

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Table 1. Main achievements in non-standard radioisotope production obtained with the STS at the Bern medical cyclotron. The integrated current corresponds to the amount of protons hitting the target material.

Isotope	Reaction	Target	Mass [mg]	Charge [μAh]	Y [GBq/μAh]
^{44}Sc	(p,n)	$^{enr-44}$CaO pellet	30	27	0.6
^{47}Sc	(p,α)	$^{enr-50}$TiO$_2$ pellet	35	3.9 E-3	0.001
^{61}Cu	(p,α)	$^{enr-64}$Zn pellet	40	2.7 E-4	0.14
^{64}Cu	(p,n)	$^{enr-64}$Ni deposition	63	160	0.13
	(p,α)	$^{enr-67}$ZnO pellet	59	2.7 E-4	0.02
^{67}Cu	(p,α)	$^{enr-70}$ZnO pellet	34	1.7 E-3	0.001
^{68}Ga	(p,n)	$^{enr-68}$Zn pellet	40	0.24	4.5
^{155}Tb	(p,n)	$^{enr-155}$Gd$_2$O$_3$ pellet	40	1.1 E-3	0.004
	(p,2n)	$^{enr-156}$Gd$_2$O$_3$ pellet	40	1.1 E-3	0.01
^{165}Er	(p,n)	^{nat}Ho metal disk	160	1.7	0.07
^{165}Tm	(p,2n)	$^{enr-166}$Er$_2$O$_3$ pellet	59	1.1	0.02
^{167}Tm	(p,n)	$^{enr-167}$Er$_2$O$_3$ pellet	41	0.01	0.003

available in form of powder or solid foils, a specific magnetic coin was conceived and realized. The coin has the same external dimension as an ordinary disk but it is composed of two halves kept together by small permanent magnets (Figure 2). It is made of an aluminum alloy (EN AW-6082) or niobium, characterised by high melting point and low residual activation. The front side is used to adjust the energy of the protons reaching the target material, the back side hosts a 6-mm-diameter pocket to host the target in form of compressed pellet or foil. An O-ring is used to prevent the leakage of molten material or any gas produced during the irradiation [5]. The body of the STS is connected to a B29885A Keysight electrometer to measure the current on-line during the irradiation. Radiochromic films [6] are used to measure the 2D beam profiles and allow to assess the effective current hitting the 6-mm pellet with an uncertainty of 10%.
Thanks to these developments, several radionuclides have been produced at the Bern medical cyclotron with solid targets, as reported in Table 1. In particular, the production of about 15 GBq of ^{44}Sc represents a very promising result in view of theranostic clinical applications [7].

3. The Automatic Focalization System

Achieving safe and reliable radioisotope production for theranostics from solid targets is challenging. On the one hand, if the beam is much larger than the target, a typical situation for medical cyclotrons, only a small fraction of it participates in the radionuclide production. The remainder causes overheating of the target and unwanted activation of the system, giving rise to radiation protection issues. On the other hand, a focused beam is very sensitive to instability, e.g. small drifts caused by heating of the cyclotron's magnetic dipole during irradiation.
To enhance irradiation performances, the Automatic Focalization System (AFS) was conceived, constructed and recently tested [8]. The AFS is composed of the Mini-PET Beamline (MBL) [9], a two-dimensional beam profiler (UniBEaM) and a software feedback system. The MBL is a 50-cm-long pipe produced by D-Pace, embedding two quadrupole and two steering magnets within the same structure. The UniBEaM detector [10] is a non-destructive two-dimensional beam profiler based on scintillating silica doped fibers passing through the beam. The working principle and the main components of the UniBEaM are reported in Figure 3. This detector was

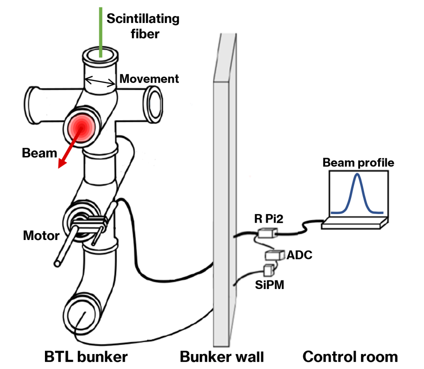

Figure 3. Schematic view of the UniBEaM detector.

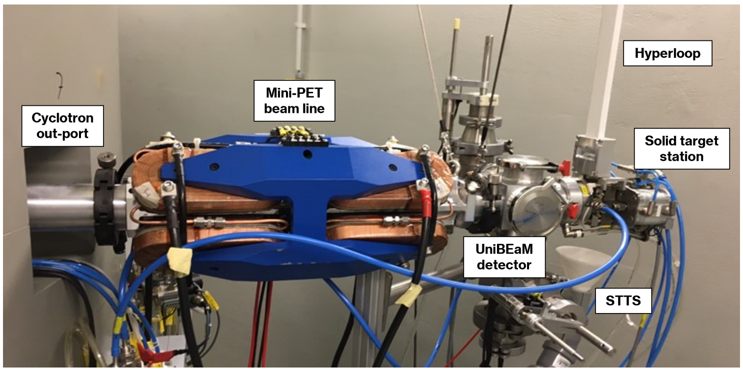

Figure 4. The automatic focalization system mounted in the cyclotron bunker.

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 [11]. A commercial version is manufactured by D-Pace [12]. The feedback system performs the analysis of the beam profile measured by the UniBEaM and, if necessary, corrects the beam position and shape by varying the currents in the power supplies of the MBL. Beam tests were successfully carried out by installing the AFS at the end of the BTL [13]. In particular, the focusing capabilities of the system were demonstrated and a gain factor of about 20 was found in the radioisotope production using solid targets [14].
The AFS was recently installed in front of the STS in the cyclotron bunker (Figure 4) and the first tests are currently ongoing. The compactness of the AFS (about 1 m long) allows its installation in any medical cyclotron.

4. Beam energy measurement

The accurate knowledge of the proton beam energy is of paramount importance for an optimized production of novel radioisotopes for medical applications, where high radionuclidic purities are required. In the out-port of the BTL, the extracted energy was accurately measured with different methods based on the assessment of the beam current after passive absorbers of different thicknesses [15], on a multi-leaf Faraday cup [16] and on Rutherford Backscattering Spectrometry [17]. A further 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 $\pm$ 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. In order to measure the energy of the beam extracted to the STS out-port, a method based on the stacked-foils technique was developed. The well known monitor reaction ^{nat}Ti(p,x)^{48}V was chosen for this purpose, being characterized by a particular shape so that the produced activity strongly depends on the beam energy [19]. Two 125 μm Nb energy degraders and six 25 μm natural Ti foils with a diameter of 13 mm were inserted in the coin pocket and irradiated. A specially designed coin with a hole in the front side was used to prevent the beam from degrading its energy. Each foil was then measured with a 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 minimization method was applied to identify the initial energy that minimizes the sum of squared residuals. This method was validated in the BTL and the beam energy measurement in the STS is currently in progress for different stripper angles.
This methodology can be easily applied to any medical cyclotron without the need of a beam transfer line.

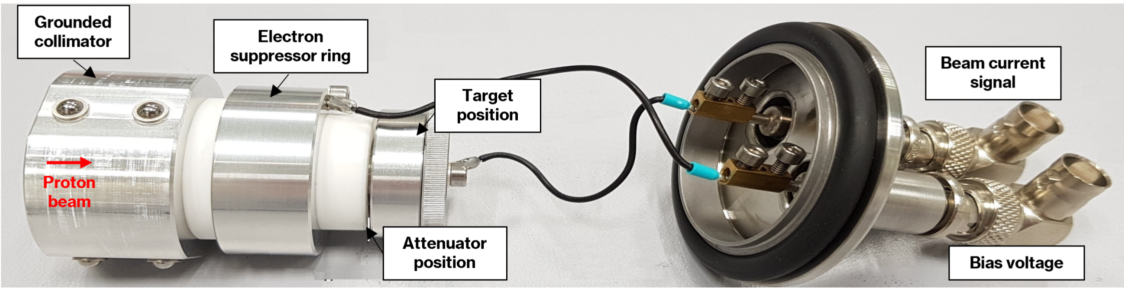

Figure 5. Target station used for cross-section measurements.

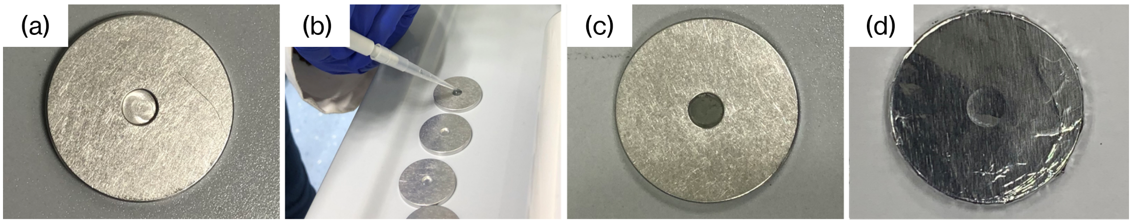

Figure 6. Preparation of targets for cross-section measurements: (a) empty aluminum disk; (b) sedimentation procedure; (c) aluminum disk filled with target material; (d) target covered with a thin aluminum foil.

5. Cross-section measurements

To maximise the production yield of the desired radionuclide while minimising the production of any impurity, it is necessary to have a precise knowledge of the cross sections of the nuclear reactions involved. A novel method was developed to measure the cross sections using targets in form of powder [20], for which the thickness homogeneity cannot be controlled. It relies on the irradiation of a known mass with a proton beam with a flat profile. The beam is flattened by the optical elements of the BTL and monitored online with the UniBEaM detector. The beam current hitting the target is measured with a custom target station (Figure 5) connected to an electrometer (B29885A Keysight). The station provides a beam of controlled diameter by means of an 8 mm grounded collimator and is equipped with an electron suppressor ring, connected to a negative potential to repel secondary electrons produced during the irradiation. To perform measurement below 18 MeV, the beam energy is degraded by aluminium attenuator disks placed in front of the target and is determined on the basis of our pristine beam energy measurement using the SRIM Monte Carlo code [21]. The produced activity is assessed by gamma spectrometry with the HPGe detector.

The target consists of a 23 mm disk, usually made of aluminum, with a 4 mm diameter and 0.8 mm deep pocket in its center (Figure 6-a). The target material is deposited by sedimentation from a suspension of a few milligrams of powder in ultra-pure water or ethanol (Figure 6-b), which is then evaporated by means of a heating plate (Figure 6-c). The target mass is assessed with an analytical balance (Mettler Toledo AX26 DeltaRange). To prevent possible leakage of the material during the irradiation and the measurement, the disk is covered by a 13 μm thick aluminum foil (Figure 6-d). With this procedure, target thicknesses of a few tens of μm are achieved and the beam energy can be considered constant within the uncertainties over the full irradiated mass.

With this method, the production cross section of several radioisotopes (^{43}Sc [20], ^{44}Sc [20], ^{47}Sc [22, 23], ^{48}V [20], ^{61}Cu [24], ^{64}Cu [25], ^{67}Cu, ^{68}Ga [26], ^{155}Tb [27], ^{165}Er [28], ^{165}Tm, ^{167}Tm and related impurities) was measured.

6. Conclusions and outlook

New irradiation instruments and procedures to measure the beam energy and the production cross sections were developed at the Bern medical cyclotron laboratory to optimise the radionuclide production for theranostics. The promising results obtained so far 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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