

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

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**Abstract.** The production of theranostic radionuclides using solid targets is challenging and requires an accurate knowledge of the production crosssections as well as the energy, positioning and focusing of the beam. A research program is ongoing at the 18 MeV Bern medical cyclotron, equipped with a Solid Target Station (STS) and a 6 m Beam Transfer Line (BTL) ending in a separate bunker with independent access. A novel target coin was designed and built to irradiate compressed powder pellets, together with a compact focalization system to optimize the irradiation procedure. Furthermore, methods were developed to measure the beam energy, the production cross-sections and the EoB-activity.

## 1 Introduction

The concept of theranostics in nuclear medicine couples diagnostic imaging and therapy, using a pair of radioisotopes with identical or very similar chemical properties to label the same biomolecule. A diagnostic radionuclide ( $\beta^+$ - or  $\gamma$ -emitter) is used to detect possible diseases, helping to predict whether the patient will benefit from the treatment imparted by the second radionuclide ( $\beta^-$ , Auger- or  $\alpha$ - emitter). Along this line, radiometals can be used to label peptides and proteins and form some of the most promising pairs as  $^{43,44}\text{Sc}/^{47}\text{Sc}$  and  $^{61,64}\text{Cu}/^{67}\text{Cu}$ . In contrast to the production of standard radioisotopes with liquid targets, as  $^{18}\text{F}$ , the production of radiometals is challenging and requires the use of new irradiation instruments and methods. In particular, rare and expensive isotope enriched materials, usually available in form of powder, have to be irradiated. For this purpose the use of solid target stations represent a possible option. A research program is ongoing at the Bern University Hospital (Inselspital) cyclotron laboratory [1], where an IBA Cyclone 18/18 HC medical cyclotron (18 MeV proton beams, max. 150  $\mu\text{A}$ , 8 out ports) is in operation. The facility is characterized by two bunkers with independent access, allowing to carry out both

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the routine industrial production of  $^{18}\text{F}$ -labeled PET tracers, performed by the spin-off company SWAN Isotopen AG, and multidisciplinary research activities. For the latter purpose, the Bern medical cyclotron is equipped with a 6 m long Beam Transfer Line (BTL) [2], bringing the proton beam to the second bunker, and an IBA Nirta Solid Target Station (STS). To enhance the cyclotron performance, an ultra compact Automatic Focalization System (AFS) based on a novel magnetic lens and a two-dimensional beam detector was recently conceived, constructed and tested [3].

## 2 Solid target developments and first results

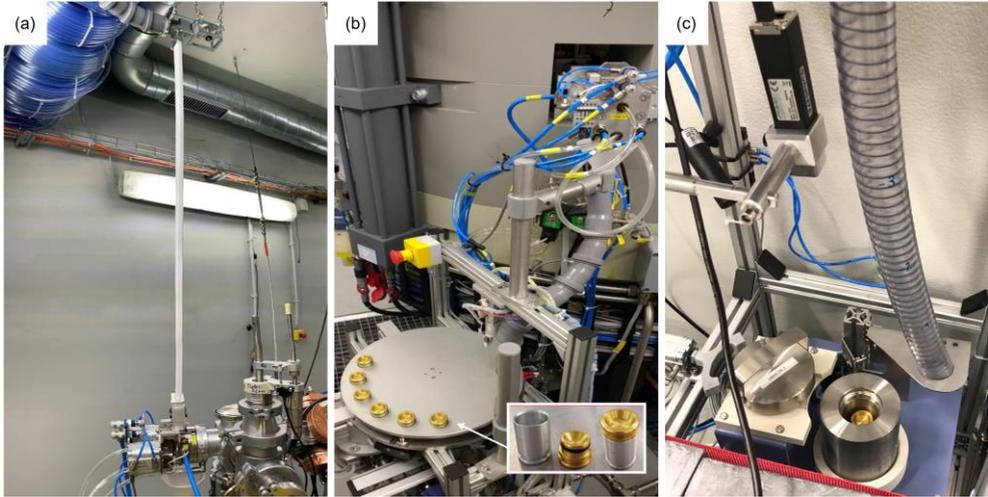
The STS was installed in one of the out ports of the cyclotron and was designed to irradiate a disk (24 mm diameter, 2 mm thick) on which the target material is electroplated. To limit overheating during irradiation, the disk is water-cooled and helium-cooled on the back and the front side, respectively. Since electrodeposition is not suitable for the production of radiometals and other interesting radionuclides, a specific magnetic coin target was conceived and realized by our group. The coin has the same external dimensions as an ordinary disk but it is made of two aluminium or niobium halves kept together by small permanent magnets (Figure 1). To optimize the produced activity and the radionuclidic purity, the material and the thickness of the front-end are used to adjust the energy of protons reaching the target. The back-end hosts the 6 mm pellet and an O-ring to prevent the leakage of molten material or any gas produced during the irradiation.



**Fig. 1.** The two halves of the coin target (24 mm diameter, 2 mm thick).

The STS was complemented with a mechanical transfer system (named Hyperloop - Figure 2-a) [4] designed by our group and with a pneumatic target transfer system (STTS) by TEMA Sinergie (Figure 2-b). The former allows to load the target station without entering the cyclotron bunker, minimizing the dose to the personnel. The latter is used to deliver the irradiated target 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 (Figure 2-c) 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  $\sim 1 \text{ cm}^3$  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 a maximum of about 50 cm from the source. Once calibrated by means of a HPGe detector, the signal of the CZT allows assessing the EoB activity with an accuracy of a few percent [5]. Thanks to these developments, several radionuclides have been produced at the Bern medical cyclotron with the STS, as reported

in Table 1. In particular, the production of about 15 GBq of  $^{44}\text{Sc}$  represents a very promising result in view of theranostic clinical applications [6].



**Fig. 2.** (a) The Hyperloop system connected to the STS. (b) The IBA Nirta solid target station and the solid target transfer system by TEMA Sinergie. A shuttle is visible in the inset. (c) The receiving station located in the BTL bunker.

Isotope	Reaction	Target	Yield [GBq/ $\mu\text{Ah}$ ]
$^{44}\text{Sc}$	(p,n)	$^{enr44}\text{CaO}$	$\sim 0.6$
$^{48}\text{V}$	(p,n)	$^{nat}\text{Ti}$	$\sim 0.015$
$^{61}\text{Cu}$	(p, $\alpha$ )	$^{enr64}\text{Zn}$	$\sim 0.021$
$^{64}\text{Cu}$	(p,n)	$^{enr64}\text{Ni}$	$\sim 0.13$
$^{68}\text{Ga}$	(p,n)	$^{enr68}\text{Zn}$	$\sim 6$
$^{155}\text{Tb}$	(p,n)	$^{enr155}\text{Gd}_2\text{O}_3$	$\sim 0.002$
$^{165}\text{Er}$	(p,n)	$^{nat}\text{Ho}$	$\sim 0.015$
$^{165}\text{Tm}$	(p,2n)	$^{enr166}\text{Er}_2\text{O}_3$	$\sim 1.2$

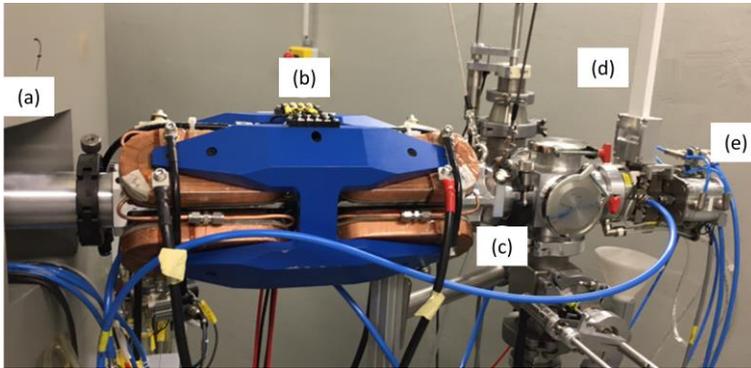
**Table 1.** Main achievements in non-standard radioisotope production obtained with the STS at the Bern medical cyclotron.

### 3 Automatic Focalization System

In most cases, STSs are mounted in out-ports of medical cyclotrons without any optical device for beam steering and focusing, resulting in an extracted beam of  $\sim 12$  mm FWHM or more on target. When our coin is used, this implies that about 75% of the extracted protons do not hit the 6 mm target material, producing overheat during the irradiation and unwanted residual activity, giving rise to radiation protection issues.

To limit unnecessary stress for the machine and enhance the irradiation performance, an Automatic Focusing System (AFS) was conceived, developed and recently tested [3]. The AFS consists of the Mini-PET Beamline (MBL) [7], a two-dimensional beam profiler (UniBEaM) and a software feedback system. The MBL is a  $\sim 50$  cm long magnet produced by the Canadian company D-Pace, embedding two quadrupole and two steering magnets within the same structure. The UniBEaM detector [8] 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 to measure the beam profile in a wide range of currents and a commercial version is manufactured by D-Pace [9]. The feedback system analyses the beam profiles measured by the UniBEaM and, if necessary, corrects the beam position and shape by varying the current in the power supplies of the MBL. Beam tests were successfully carried out by installing the AFS at the end of the BTL; in particular we demonstrated the focusing capabilities of the system and a gain factor of about 20 was found in the production of radioisotope using solid targets [3]. The AFS was recently installed in front of the STS in the cyclotron bunker (Figure 3) and the first tests are presently ongoing.

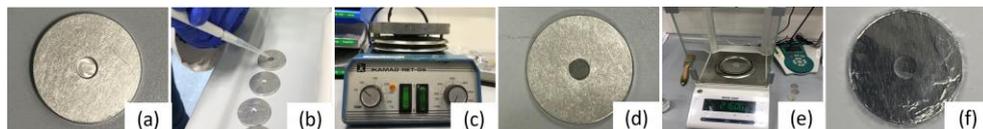


**Fig. 3.** The Automatic Focalization System installed in the cyclotron bunker: (a) cyclotron out-port; (b) Mini-PET beam line; (c) UniBEaM detector; (d) target receiving station of the Hyperloop; (e) Solid Target Station.

## 4 Cross section measurements

For an optimized radioisotope production, a precise knowledge of the reaction cross sections is crucial and a novel method for their measurements was developed by our group using targets in form of powder [10, 11]. In most cases, the powder is deposited on an aluminium disk 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 a commercial version of the UniBEaM detector. The beam current hitting the target is measured by means of a custom target station composed of a 6 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 better than 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 on target are performed throughout each irradiation by connecting the target holder to an ammeter (B29885A Keysight). The conductive parts of the target station are kept together by insulator components. The beam energy is degraded by means of aluminium attenuator disks placed in front of the target and is determined using the SRIM Monte Carlo code [12]. The produced activity is assessed by gamma spectroscopy with an 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 4-a). The target material is deposited by sedimentation from a suspension of a few milligrams of material in ultra-pure water or ethanol, which is then evaporated by means of a heating plate (Figure 4-b - Figure 4-d). The target mass is assessed with an analytical balance (METTLER TOLEDO AX26 DeltaRange, Figure 4-e). To prevent the escape of the material during the irradiation and the measurement procedure, the disk is covered by a 13  $\mu\text{m}$  thick aluminum foil (Figure 4-f). With this method, the production cross section of several radioisotopes ( $^{43}\text{Sc}$ ,  $^{44}\text{Sc}$  [10],  $^{47}\text{Sc}$  [11],  $^{48}\text{V}$  [10],  $^{61}\text{Cu}$ ,  $^{68}\text{Ga}$ ,  $^{155}\text{Tb}$ ,  $^{165}\text{Tm}$  and related impurities) was measured.



**Fig. 4.** Preparation of a target for cross section measurements: (a) empty aluminum disk; (b) sedimentation procedure; (c) heating plate; (d) aluminum disk filled with target material; (e) analytical balance; (f) aluminum disk covered with a thin aluminum foil.

## 5 Beam energy measurement

The energy of the proton beam is another essential parameter for an optimised radioisotope production with solid targets. The energy measurement of the beam extracted on the STS is currently ongoing with a method based on the stacked-foil technique. The well known monitor reaction  $^{nat}\text{Ti}(p,x)^{48}\text{V}$  was chosen for this purpose, being characterized by a particular shape so that the produced activity strongly depends on the beam energy [13]. Two stacks composed of natural Ti thin foils, separated by a Nb energy degrader, are positioned in the coin pocket and irradiated. Each foil is then measured with a well calibrated HPGe detector, whose counting efficiency is known with an uncertainty less than 5%. Knowing the produced activity, the  $^{48}\text{V}$  production cross section can be estimated for several initial proton energies, allowing to determine which energy best reproduces the experimental data. This method has been validated in the BTL, where the extracted beam energy was measured to be  $(18.3 \pm 0.3)$  MeV, in good agreement with the measurements we performed with other methods [14, 15].

## 6 Conclusions and outlook

In the framework of the research program on the production of theranostic and non standard radioisotopes ongoing at the Bern medical cyclotron, new instruments and methods were developed. A novel automatic focusing system was conceived, constructed and tested, together with new non-destructive beam monitoring detectors and a novel target coin to irradiate solid materials. New procedures to measure the nuclear cross sections, the beam energy and the produced activity at EoB were also developed.

These developments and findings lead to promising results that will be instrumental in view of the use of novel radioisotopes for theranostics in nuclear medicine.

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