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Research on theranostic radioisotope production at the Bern medical cyclotron

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Summary. — The production of medical radioisotopes for theranostics is essential for nuclear medicine developments. A research program is ongoing at the 18 MeV Bern medical cyclotron, where a solid target station is in operation together with a 6.5 m Beam Transfer Line (BTL) ending in a separate bunker. To irradiate compressed powder pellets, novel target coins were conceived and realized together with methods to assess the beam energy and the production cross-sections. The activity at the end of the beam (EOB) is measured with a 1 cm^3 CdZnTe detector. An ultra-compact active irradiation system based on a novel focusing and steering magnet and two-dimensional beam detectors is under development. Results on ^{43}Sc, ^{44}Sc, ^{47}Sc, ^{61}Cu, ^{64}Cu, ^{68}Ga, ^{155}Tb, ^{165}Er and ^{165}Tm production are presented.

1. – Introduction

Novel radioisotopes are essential for the future development of personalized nuclear medicine. The theranostic approach is based on a pair of isotopes with very similar or identical chemical properties, one for diagnosis and one for therapy. They can be used to label the same or very similar biomolecules that undergo the same metabolic processes within the patient body. In this way, they allow treating the disease and, at the same time, assessing the uptake in the tissues and following the evolution of the therapy. In this paper we report about some of the developments and results obtained in the framework of the research programs on-going at the Bern University Hospital (Inselspital) cyclotron laboratory [1]. The facility is based on an IBA Cyclone 18/18 high current cyclotron (18 MeV proton beams, max. 150 μA extracted current, 8 out ports), equipped with an IBA Nirta Solid Target Station (STS), a 6.5 m long external Beam Transfer Line (BTL) and two bunkers with independent access. This solution is unusual for a hospital-based facility and was conceived to perform both routine industrial production of ^{18}F labeled PET tracers and multidisciplinary research activities by means of the BTL.

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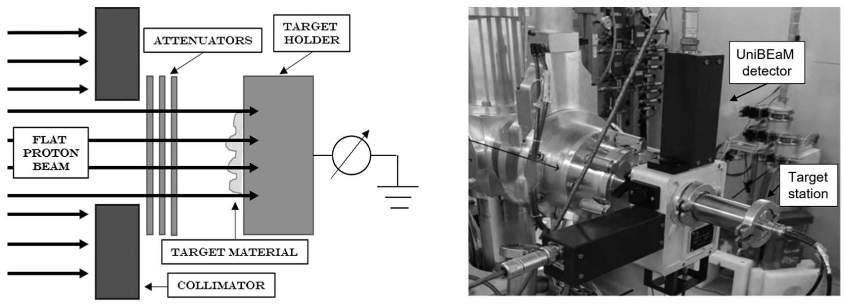

(a) (b)

Fig. 1. – (a) New cross-section measurement procedure based on a flat beam current surface density developed by our group. (b) Experimental set-up for cross-section measurements.

2. – Cross-section measurements

A novel method to measure cross-sections with a medical cyclotron was developed [2]. It is based on the irradiation of a known target mass with a proton beam with a flat profile (fig. 1(a)) instead of the usual method relying on the irradiation of a uniformly thick target. The beam is flattened by the optical elements of the BTL and monitored on-line with the UniBEaM detector [3] (fig. 1(b)), based on silica doped fibers passing through the beam. This beam profiler was developed by our group and is commercialised by the Canadian company D-Pace [4].

The beam current passing through the collimator is measured in real time by using a custom target station designed and built by our group (fig. 1(b), fig. 2). The station's main components are: a 6 mm diameter collimator connected to ground; an electron suppressor ring, connected to a negative bias voltage in order to repel secondary electrons produced during the irradiation; a target holder, connected to an ammeter for current measurements on target. Before hitting the target, the beam crosses thin aluminum discs used to degrade its energy, that is calculated by Monte Carlo simulations (SRIM). The obtained activity is measured by High-Purity Germanium (HPGe) gamma spectroscopy. The efficiency of the detector was assessed using a multi-gamma source, the activity of which is known with an uncertainty below 1%. With this method, the production cross-section of several radioisotopes (^{43}Sc, ^{44}Sc [2, 5], ^{48}V [2], ^{44m}Sc, ^{66}Ga, ^{67}Ga, ^{68}Ga [6], ^{154}Tb, ^{155}Tb, ^{156}Tb, ^{165}Tm, ^{166}Tm, ^{167}Tm and ^{47}Sc, ^{48}Sc, ^{47}Ca [7]) was measured.

3. – Solid target developments and future prospects

The STS is installed on one out port of the cyclotron together with a pneumatic transfer system (STTS) by TEMA Sinergie (fig. 3(a)). The STTS was customized in the way that the shuttle containing the irradiated target can be sent either to one hot

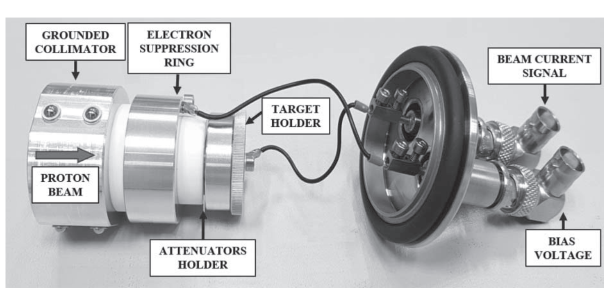

Fig. 2. – Target station used for the cross-section measurements.

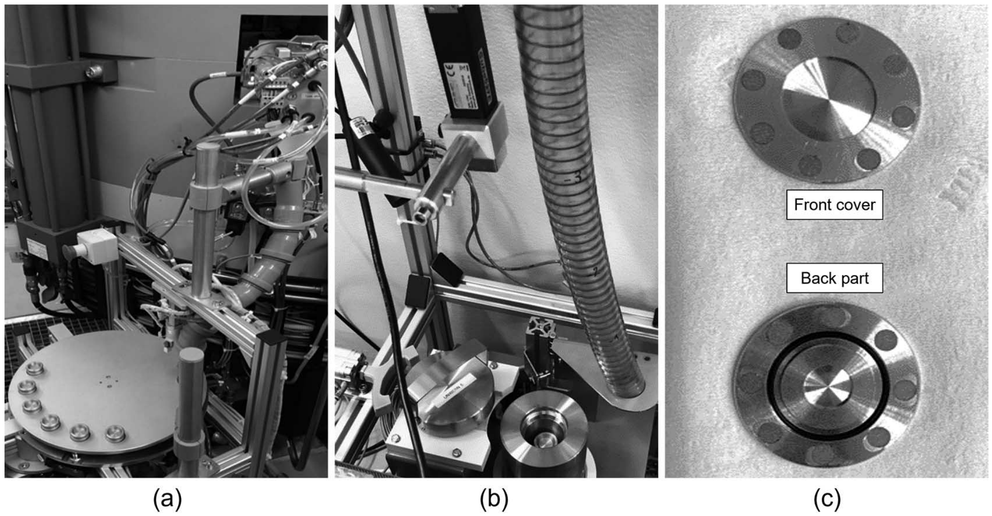

Fig. 3. – (a) The IBA Nirta solid target station and the solid target transfer system by TEMA Sinergie installed on the Bern medical cyclotron. (b) The receiving station located in the BTL bunker. (c) The coin target (24 mm diameter, 2 mm thick).

cell in the nearby GMP radio-pharmacy, or to a receiving station located in the BTL bunker (fig. 3(b)). The STS was designed to irradiate a disk (24 mm in diameter, 2 mm thick) on which the target material is electroplated. To irradiate materials in form of compressed powders or solid foils, a specific target coin was conceived and built by our group (fig. 3(c)). The thickness of the coin front window is used to adjust the energy of the protons reaching the target material. Thanks to an accurate knowledge of cross-section, this leads to an optimization of the produced activity and the radionuclidic purity. The back part contains the 6 mm pellet and completely stops the protons. An O-ring is embedded in the coin to prevent the escape of molten material or any gas produced during irradiation. To experimentally assess the produced activity after EoB, a CZT detector system was designed and installed in the receiving station (fig. 3(b)). Based on a $\sim$1 cm^3 CdZnTe crystal (GBS Elektronik), this detector allows recording the energy spectra of the gamma rays emitted by the target. The position of the detector with respect to the source can be modified by means of an automatic motor, up to a maximum of about 50 cm. The low detection efficiency due to the distance and the small volume of the crystal allows to measure the high produced activities, limiting the undesired effects of high counting frequencies, like dead time, pulses pile up etc.

The detector has been experimentally calibrated in energy and efficiency and its signal allows measuring the produced activity with an accuracy of a few per cent [8]. Thanks to these developments, several radionuclides have been produced at the Bern medical cyclotron with the solid target station, as reported in table I. In particular, the production of about 15 GBq of ^{44}Sc represents a very promising result in view of theranostic clinical applications [9].

Being the beam extracted from the cyclotron $\sim$12 mm FWHM at the STS, about only 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, giving rise to specific radiation protection measures and transport limitations. To enhance the irradiation performance, a novel irradiation system based on an ultra-compact beam line

TABLE I. – *Main achievements in non-standard radioisotope production obtained with the STS at the Bern medical cyclotron. The current corresponds to the protons hitting the target material.*

Isotope	Reaction	Target	Current [μA]	Irr. Time [h]	A_{EOB} [GBq]
^{44}Sc	(p,n)	^{enr44}CaO pellet	5	5	~15
^{48}V	(p,n)	^{nat}Ti metal foil	10	1	~0.15
^{61}Cu	(p,α)	^{enr64}Zn pellet	25	1.9	~1
^{64}Cu	(p,n)	^{enr64}Ni deposition	15	10	~20
^{68}Ga	(p,n)	^{enr68}Zn pellet	5	0.5	~15
^{X}Pm	(p,X)	^{nat}Nd disc	5	3	$\sim 10^{-7}$
^{155}Tb	(p,n)	^{enr155}Gd pellet	2.5	1.15	~0.005
^{165}Er	(p,n)	^{nat}Ho metal disk	10	10	~1.5
^{165}Tm	(p,2n)	^{enr166}Er$_2$O$_3$	2.5	0.5	~1.5

(about 1 m long) and two-dimensional beam monitoring detector is under development. This system will focus the beam down to the diameter of the pellet and will likely improve the production yield and minimize unwanted radiation protection and handling issues. Being compact, this system can be installed in any medical cyclotron facility.

4. – Conclusion and outlooks

A research program aimed at the production of theranostic and non-standard radioisotopes is on-going at the Bern medical cyclotron laboratory. Thanks to developments in accelerator and detector physics, new methodologies and instrumentation were developed. The promising results obtained up to now represent an important milestone in view of the use of medical cyclotrons for theranostics and personalized nuclear medicine.

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