ACCELERATOR AND DETECTOR DEVELOPMENTS FOR THE PRODUCTION OF THERANOSTIC RADIOISOTOPES WITH SOLID TARGETS AT THE BERN MEDICAL CYCLOTRON

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Abstract

Theranostics in nuclear medicine is realized by using two different radionuclides to label the same radiopharmaceutical, one for diagnosis via PET or SPECT (positron or gamma emitter, respectively) and one for targeted radioligand therapy (alpha, beta minus, Auger emitter). To assure the same chemistry and metabolic behaviour in the human body, the best option is to employ two radioisotopes of the same element, the so called theranostic pair. In view of clinical trials and routine applications, the production and supply of novel radioisotopes for theranostics in adequate quality and quantity is essential and represents nowadays a scientific and technical challenge. The most promising methodology relies on hospital-based 15-25 MeV compact medical cyclotrons equipped with solid target stations. Being designed for the production of ^{18}F by means of liquid targets, innovative solutions are needed. Therefore, a research program is ongoing at the Bern medical cyclotron, a facility 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 (6 mm diameter), 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 Focusing System based on a specific magnetic device and a two-dimensional beam monitoring detector was conceived, constructed and tested. Several solutions for the beam detector were developed and others are under study. 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. Results on accelerator and detector developments together with achievements in the production of radionuclides for theranostics (^{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.

INTRODUCTION

To enhance the availability of novel medical radioisotopes that can be used as theranostic pairs is crucial for the advancement of nuclear medicine. Theranostic pairs consist of two complementary radionuclides; a β^+ or γ emitting radionuclide is used for diagnosis via PET or SPECT imaging respectively, while the other radionuclide undertakes the radioimmuno-therapeutic task of emitting β^-, Auger, or α particles. These radionuclides must have similar or identical chemical properties, as in the case of isotopes of the same element. They can be used to label the same biomolecules, which are then injected into the patient's body and undergo the same metabolic processes. This allows for the treatment of the disease while simultaneously assessing uptake and monitoring the progress of the therapy through medical imaging. Examples of promising theranostic pairs include ^{43,44}Sc/^{47}Sc and ^{61,64}Cu/^{67}Cu, which are bound to proteins and peptides.

The availability of these radionuclides is a limiting factor in the development of theranostics in nuclear medicine. One solution is to utilize compact medical cyclotrons for the radionuclides' production, as they are commonly installed at medical institutions. Medical cyclotrons produce proton beams of low energy (15-20 MeV) and relatively high intensity (>100 μA). They are primarily used to produce ^{18}F - the most common PET radioisotope - through irradiation of liquid targets. However, to produce radiometals, rare and expensive isotope-enriched materials must be bombarded, which are often only available in powder form. To obtain high yields, solid target stations represent the best solution. These solid target stations, however, are rare and are typically designed to irradiate target 'disks' on which the enriched material is electroplated, a method not suitable for the production of various radiometals. Therefore, new irradiation instruments and methods must be developed to bombard compressed materials in powder form and in small dimensions of 6 mm diameter and smaller.

At the Bern University Hospital's cyclotron laboratory, research programs are ongoing to address these challenges and develop new solutions. The facility is equipped with an IBA Cyclone 18/18 medical cyclotron (18 MeV proton beams, maximum extracted current of 150 μA, 8 output ports). Six outports are used for routine production of ^{18}F at night, while the other two are used for multidisciplinary research during the day. One of the research outports is equipped with a 6.5 m long Beam Transport Line leading to a second bunker with separate access, which facilitates daily research. This is uncommon for a hospital-based facility but has been essential to achieve the results reported in this paper. The second research outport is equipped with a commercial IBA Nirta Solid Target Station (STS). This STS was customized by our group and upgraded to optimize

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usability and efficiency, and is also part of several ongoing research projects, as also reported in this paper.

SOLID TARGET STUDIES

Target Coin

To irradiate solid targets for research on theranostic pairs of radionuclides we use an IBA Nirta STS. It is a commercial product that has been designed for the irradiation of disk shaped targets of 24 mm diameter and 2 mm thickness. Since several radiometals of theranostic interest are obtained from the irradiation of pellets of compressed powder (e. g. $CaCO_3$ or CaO irradiation for the production of scandium isotopes), our group conceived and produced a particular ‘coin’ target disk [1]. The coin is composed of two halves made from high purity aluminium and held together by permanent SmCo magnets that are arranged around the the disk’s edges. Its size is of the same dimension as the intended STS targets. At the coin’s centre a special cavity is placed, which leaves space for the containment of compressed powder pellets. Both, to bring the target coin into the STS before the irradiation and to bring it out again after an irradiation, respective remotely controllable systems have been installed. Coins can be loaded into the STS from outside the cyclotron’s bunker with a custom system called *Hyperloop* [2]. To off load the coin safely after an irradiation, the STS is equipped with a commercially available pneumatic Solid Target Transfer System (STTS) by TEMA Sinergie.

Cross Section Measurements

To perform cross section measurements on the beam transfer line (BTL) a specific target station has been designed [4]. With the aid of these solid target irradiation set-ups several cross section measurements have been performed on isotopes of radiometals relevant for theranostics. A list of measured cross sections is shown in Table 1 (table taken from [3]). Additionally, studies have been performed for the isotopes ^{47}Sc [5] and ^{67}Cu [6], and are ongoing for ^{43}Sc and ^{167}Tm.

CURRENT HARDWARE DEVELOPMENTS

Our existing infrastructure at the Bern medical cyclotron, i.e. the STS and the BTL beam line are part of a constant improvement process where new devices and methods are tested with the aim of optimizing the production of radioisotopes. The latest projects are shortly described in the following section:

Automatic Focusing System

A device which is in advanced progress is the so-called Automatic Focusing System (AFS) [7, 8]. It’s main goal is to enhance the production of non-conventional medical radioisotopes using solid targets. The first prototype of the AFS has been installed and tested on the BTL. It’s integral part is an algorithm that calculates the optimal control currents of a Mini-PET beam line’s quadrupole focusing magnets, provided by the Canadian company D-Pace, by means of real time beam shape measurements it obtains from a 2D beam monitoring device, such as the Pi2 detector or a two-dimensional UniBEaM detector [9]. The algorithm is capable of optimising the beam focus for a requested target geometry and, furthermore, it can also restore beam focus on target in the case of occurring perturbations. With irradiations performed at the BTL it could be shown that the yield of ^{66,67}Ga isotopes could be improved by a factor 20 with the usage of the AFS. After successful tests on the BTL, the AFS has also been installed on the STS outport, as shown in Fig. 1. This installation needs to undergo some optimisations, though, as in comparison to the BTL installation the proton beam’s drift space is reduced and the algorithm needs to be updated. Furthermore, it is planned to replace the currently installed UniBEaM detector as the beam monitoring feedback device. The main reason for this is that the UniBEaM’s beam detecting optical fibres are potentially unsuitable for high dose irradiations as they could melt under currents larger than 20 µA. Potential candidates that could serve as beam monitoring devices are e.g. the Pi2 detector or an apparatus called *Collar*, both of which are currently

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. The table is taken from [3].

Isotope	Reaction	Target	Mass [mg]	Charge [µAh]	Y [GBq/µAh]
^{44}Sc	(p, n)	^{enr44}CaO pellet	30	27	0.6
^{47}Sc	(p, α)	$^{enr50}TiO_2$ pellet	35	3.9e-3	0.001
^{61}Cu	(p, α)	^{enr64}Zn pellet	40	2.7e-4	0.14
^{64}Cu	(p, n)	^{enr64}Ni deposition	63	160	0.13
	(p, α)	^{enr67}ZnO pellet	59	2.7e-4	0.02
^{67}Cu	(p, α)	^{enr70}ZnO pellet	34	1.7e-3	0.001
^{68}Ga	(p, n)	^{enr68}Zn pellet	40	0.24	4.5
^{155}Tb	(p, n)	$^{enr155}Gd_2O_3$ pellet	40	1.1e-3	0.004
	(p, 2n)	$^{enr156}Gd_2O_3$ pellet	40	1.1e-3	0.01
^{165}Er	(p, n)	^{nat}Ho metal disk	160	1.7	0.07
^{165}Tm	(p, 2n)	$^{enr166}Er_2O_3$	59	1.1	0.02
^{167}Tm	(p, n)	$^{enr167}Er_2O_3$	41	0.01	0.003

being developed by our group and are outlined in following sections in this paper.

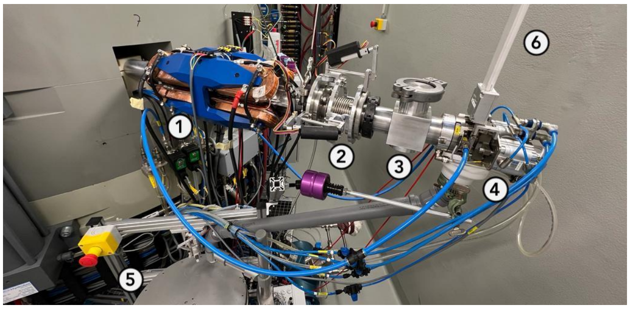

Figure 1: STS with AFS installed on the Bern medical cyclotron. 1: Mini-PET beam line, 2: Bellow++, 3: Space for beam monitoring device, 4: target holder, 5: Solid target transfer system (STTS), 6: Hyperloop target loading system.

Beam Monitoring

The UniBEaM beam monitor detector is a device developed by our group and commercialised by D-Pace. It is our go-to device for beam monitoring. Besides the UniBEaM detector also other instruments are being tested or under development:

Pi2 Detector The Pi2 detector is a beam monitoring device which is based on a coated thin aluminium foil. A picture of the detector installed on the BTL is shown in Fig. 2. The foil's P47 coating scintillates visible light when irradiated, which is then observed with a camera to evaluate the transverse position, shape, and the intensity of the beam by means of the analyzed camera output. A pneumatic system allows for the coated aluminium foil to be inserted into and removed from the proton beam, such that the beam is only minimally intrusive to the proton beam. The development of the device is in its final stages and the corresponding paper is in preparation.

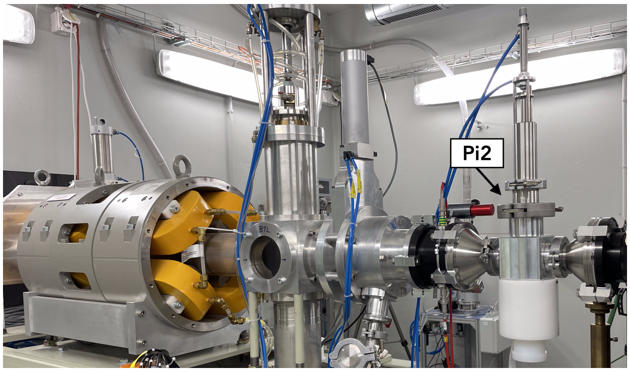

Figure 2: The Pi2 beam monitoring device installed on the BTL beam line during an irradiation.

Collar In a collaboration with TRIUMF [10] and D-Pace the development of a novel, totally non-beam invasive device called Collar is ongoing. On the basis of doped silica fibres responding to secondary radiation emitted from a respective target, the device can potentially help to give information about beam orientation and beam focusing without directly interacting with the proton beam itself, since the fibres are only mounted on the outside of the respective target and not in the actual beamline.

FURTHER MEASUREMENTS AND IMPROVEMENTS

Beam Energy Measurement

When irradiating solid targets, besides knowing the shape, direction and intensity of the proton beam, it also very important to know the exact proton energy. To accurately measure this quantity, our group made use of a technique using the well known $^{nat}\mathrm{Ti(p,X)}^{48}\mathrm{V}$ monitor reaction. Stacks of thin titanium layers are separated by an energy absorbing Nb-layer and placed in a special target coin. The number of layers per stack as well as the thickness of the layers is configured in a way, such that the layers are irradiated at energies where the monitor reaction's cross section gradient is the steepest. Additionally to the current on target, each layer's activity is then measured by gamma spectroscopy and compared to theoretical activities that are calculated for several initial beam energies. Using a least square fit, the proton beam's energy is then determined within uncertainties. The method has been tested and implemented for the BTL and a beam energy of 18.28 ± 0.05 MeV has been measured [11]. Beam energy measurements for the STS are in progress and a publication is soon to be released.

Bellow++

The STS has been very recently upgraded with an additional tool which will help in the optimisation of the beam steering and focusing, and enhance the usability of the target station. Regular maintenance works on the cyclotron's hardware can lead to changes to the extracted proton beam's geometry. Since the STS only has a limited drift space, there are limits set with regard to focusing and steering capabilities of the Mini-PET beam line. To change the absolute position of the target, a remotely controllable bellow has been installed on the beam line, as can be seen in Fig. 1. Two linear motors can move the target with respect to the outport independently in horizontal and vertical direction. A range of motion of ±5 mm in both directions is enough to compensate for the potentially occurring deviations in the beam's extraction geometry. The device is being tested and the controlling software is under development.

CONCLUSION

The Bern cyclotron laboratory is currently conducting a research program focused on the production of nonconventional radioisotopes. Besides studies on the production of novel radioisotopes for theranostic applications the program involves the development and testing of novel instruments for beam monitoring and methods based on advancements in accelerator and detector physics. The successful results obtained so far represent a significant advancement towards the goal of establishing efficient and reliable radioisotope supply using compact medical cyclotrons for theranostic applications in nuclear medicine.

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