Preliminary results of the experimental cross sections of the long-lived β^+ emitters of interest in PET range verification in proton therapy at clinical energies.

Teresa Rodriguez-Gonzalez[1,2*], *Carlos* Guerrero[1,2**], *Claus Maximilian* Bäcker[3,4,5,6], *Christian* Bäumer[3,4,5,6,7], *Walter* Jentzen[5,6,8], *M. Carmen* Jiménez-Ramos[2], *M. Ángeles* Millán-Callado[1,2], *Beate* Timmermann[4,5,6,7,9], and *José Manuel* Quesada[1]

[1]Dept. de Física Atómica, Molecular y Nuclear. Universidad de Sevilla. Avda. Reina Mercedes s/n, Seville 41012, Spain.
[2]Centro Nacional de Aceleradores (Universidad de Sevilla-Junta de Andalucía-CSIC). C/ Thomas Alva Edison 7, Seville 41092, Spain.
[3]TU Dortmund University, Faculty of Physics, Otto-Hahn-Str. 4a, D-44227 Dortmund, Germany.
[4]West German Proton Therapy Centre Essen, Hufelandstr. 55, D-45147 Essen, Germany.
[5]West German Cancer Center, Hufelandstr. 55, D-45147 Essen, Germany.
[6]University Hospital Essen, Hufelandstr. 55, D-45147 Essen, Germany.
[7]German Cancer Consortium (DKTK), Heidelberg, Germany.
[8]University Hospital Essen, Clinic for Nuclear Medicine, Hufelandstr. 55, D-45147 Essen, Germany.
[9]University Hospital Essen, Department of Particle Therapy, Hufelandstr. 55, D-45147 Essen, Germany.

Abstract. In proton therapy, offline PET range verification requires a comparison of the measured and expected β^+ activity distributions produced by the proton field in the body, looking at the the long-lived β^+ emitters. The reliability of the expected activity distributions depends on the Monte Carlo simulations and hence on the accuracy of the underlying cross section data. However, several studies confirm the need for more and better measurements and evaluations of these cross sections.

In this work, the employed method to measure the production yields of the long-lived β^+ emitters of interest in PET range verification ^{11}C ($t_{1/2}$ = 20 min), ^{13}N ($t_{1/2}$ = 10 min) and ^{15}O ($t_{1/2}$ = 2 min) in C, N and O is presented. The method combines the multi-foil activation technique with the subsequent measurement of the induced activity in a clinical PET scanner. The preliminary results of the $^{12}C(p,pn)^{11}C$ reaction cross sections is presented.

* Corresponding author: mrodriguezg@us.es
** Corresponding author: cguerrero4@us.es

1 Motivation and objective

In comparison to conventional radiation therapy, ion beam therapy is able to reduce the deposited dose in the healthy tissues close to the tumor, due to the characteristic dose distribution of the charged particles in the body of the patient. The proton dose distribution is defined by its maximum dose deposition near the end of the beam range (Bragg peak) and its finite penetration in matter [1]. Despite the mentioned benefits, current treatment plannings have to consider significant safety margins associated to the uncertainties in the actual beam range, due to several physical effects [2].

In this context, Positron Emission Tomography (PET) range verification has been proved to be a well-suited technique to monitor the range of the proton beam. This technique consists in the measurement of the activity distribution induced in the body of the patient with a PET scanner, just after the treatment (using long-lived isotopes, with a half-life of ∼min) or during the treatment (using short-lived isotopes, with a half-life of ∼ms and ∼s) [3]. The use of short-lived isotopes (in-beam range verification) would provide immediate feedback on the dose delivery and avoid the washout effect, which are the main limitations of offline (i.e. delayed) range verification [4] [5]. However, clinically, the implementation of a PET scanner for real-time imaging requires technology and device development, while offline PET range verification can be simply implemented using a conventional PET scanner close to the treatment room.

In addition, PET range verification requires the comparison of the measured activity distribution with a simulated one [6] [4], whose accuracy depends on the accuracy of the underlying cross section data for producing the β^+ emitters of interest. This work is focused on the production of the long-lived isotopes ^{11}C ($t_{1/2}$=20.4 min), ^{13}N ($t_{1/2}$=9.97 min) and ^{15}O ($t_{1/2}$=122 s), of interest in offline PET range verification. The corresponding data currently available show significant discrepancies and indeed several studies [2] [7] confirm the need for more accurate measurements. This work aims to improve the knowledge of the production cross section of the mentioned long-lived β^+ emitters at clinical energies. Furthermore, a parallel experimental campaign is focused on measuring the production cross section of the short-lived isotopes on interest in real-time PET verification.

2 Experimental set-up

The methodology followed for this purpose combines the multi-foil activation technique with a PET scanner [9]. Using a multi-foil activation, it is possible to obtain the production yields at different energies with a single irradiation, as the proton beam energy decreases as it traverses the different foils and hence the activation occurs at a different proton energy in each of them. Then, the simultaneous measurement of the irradiated films by a PET scanner allows to minimize the systematic errors associated to the measurement of the activity.

2.1 Irradiations at the West German Proton Therapy Center (WPE)

The experiment was carried out in one of the clinical treatment rooms at the West German Proton Therapy Center, in Essen (Germany). The number of protons per Monitor Unit (MU) is measured with an ionization chamber. The pencil beam scanning (PBS) mode is used for the activation of the target.

Three multi-foil targets rich in carbon (polyethylene), oxygen (silicon dioxide) and nitrogen (aluminium nitride) were irradiated (see Figure 1, left). The thickness was 1 mm for

the PE and SiO_2 foils and 0.64 mm for the AlN foils. These thin foils were embedded between thicker foils of polyethylene, which serve to degrade the proton beam energy. The thickness of these degraders is 5 and 10 mm, depending the initial beam energy, to minimize the number of irradiations, thus saving beam time, money and reducing systematic errors . As an example, Figure 2 displays the proton energy distribution for the PE foils calculated with Geant4 [10] for different initial beam energies.

The first foil in each stack is a PMMA *monitor* film, which serves to validate at the same time the measurement of the relative beam intensity and the calculations of the decay during

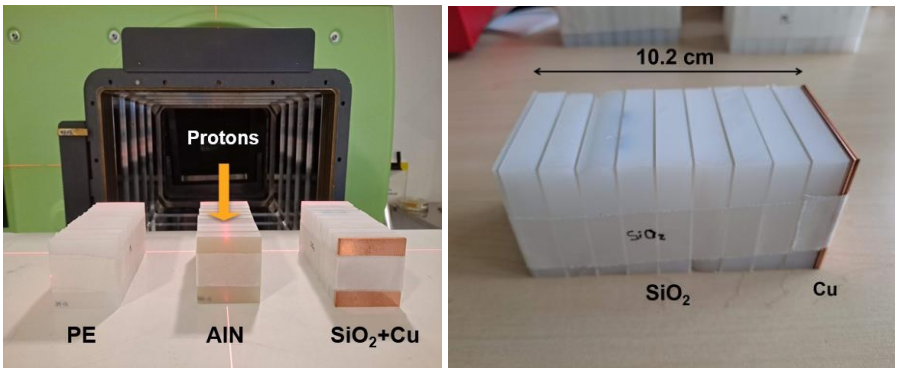

Figure 1. Left: Experimental setup during the irradiations. Right: The SiO_2 stack made of 10 thin foils of SiO_2 between thicker PE degraders. The first and last foils are the PE monitor foil and copper, respectively.

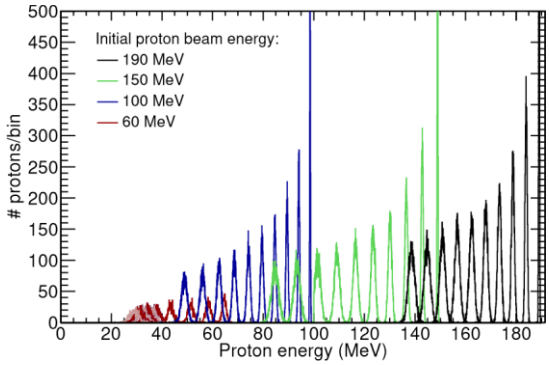

Figure 2. Proton energy distribution for the PE assembly. Note that in the case of the 60 MeV irradiation, a 100 MeV proton beam was degraded using 40 mm of polyethylene. In this case, the different intensities of red colour is used to distinguish between consecutive distributions.

the irradiation and during the transport from the treatment room to the PET scanner. A copper target was also placed at the end of the SiO_2 stack to ensure the validation of the results comparing with the IAEA monitor reaction of reference $^{nat}Cu(p,x)^{63}Zn$ [11]. A picture of the target assembly is shown in Figure 1 (right). Before each irradiation, radiochromic foils EBT3 were placed at the same place than the target foils to ensure the position and size of the beam spot.

2.2 Measurement of the induced activity with a clinical PET/CT scanner

For each initial beam energy, the activity of all foils was measured simultaneously using a PET scanner in dynamic acquisitions of 60 s during 4 hours. In total, 10 foils of PE, 10 foils of AlN, 10 foils of SiO_2, the monitor foils and copper were embedded in thicker plates of polyethylene, to ensure the conversion of the positron emitted into two 511 keV photons. In Figure 3, the polyethylene plates containing the irradiated foils and the PET measurement are shown.

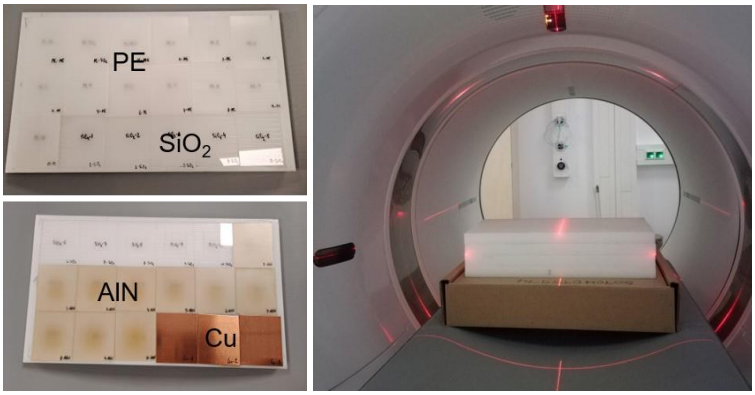

Figure 3. PET/CT measurement of the irradiated foils embedded between polyethylene plates.

The calibration of the PET scanner was performed using a ^{22}Na calibrated source. The uncertainty in the spatial PET efficiency was considered to be 3%, after measuring with sources of different activities in different positions.

3 Analysis and preliminary results of the reaction cross section ^{12}C(p,n)^{11}C

The reaction cross section was obtained from the induced activity at the end of bombardment (EOB). Taking into account the decay constant of ^{11}C, ^{13}N and ^{15}O, the activity curves obtained with the PET/CT scanner are fitted to:

$$A(t) = c + A_{^{11}C}^{EOB} e^{-\lambda_{^{11}C} t} + A_{^{13}N}^{EOB} e^{-\lambda_{^{13}N} t} + A_{^{15}O}^{EOB} e^{-\lambda_{^{15}O} t}. \quad (1)$$

In equation 1, $\lambda_i = ln(2)/t_1{}^i{}_{/2}$ and A_i^{EOB} is the activity at EOB, for i each isotope of interest, and c is a constant, that has been proved to be negligible in all cases.

The reaction cross section is then calculated as:

$$\sigma(E_i) = \frac{Y_i(E_i) \cdot c_{decay}}{\lambda \cdot n_i} = \frac{(A^{EOB}/C) \cdot c_{decay}}{\lambda \cdot n_i}, \quad (2)$$

where n_i is the number of nuclei per unity of area, C is the total charge, λ is the decay constant. The induced activity is corrected by the decay during the irradiation process and during the transportation to the PET/CT scanner:

$$c_{decay} = \frac{\lambda T_{irrad}}{1 - e^{-\lambda T_{irrad}}} \quad (3)$$

The analysis of the monitoring foils of polyethylene indicates an agreement between the corresponding A_{EOB} within 1.7% (see Figure 4), which in then considered the uncertainty related to the reproducibility of the irradiations. The good agreement validates also the decay corrections and beam current measurement.

The production cross sections of ^{11}C, ^{13}N and ^{15}O in C, N and O has been measured using this technique. The preliminary cross section of $^{12}C(p,n)^{11}C$ is shown in Figure 5, together with the available data sets in the EXFOR data base [8]. The results presented herein are in

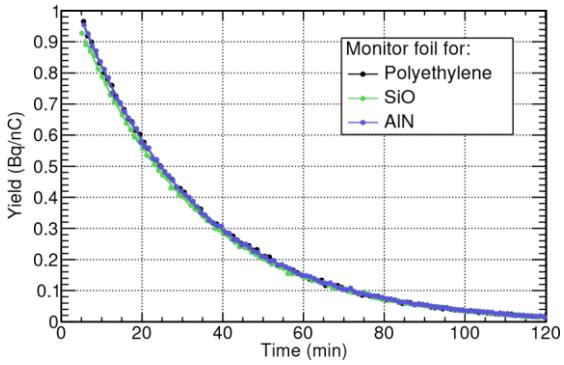

Figure 4. Decay curves of the monitoring foils at 60 MeV.

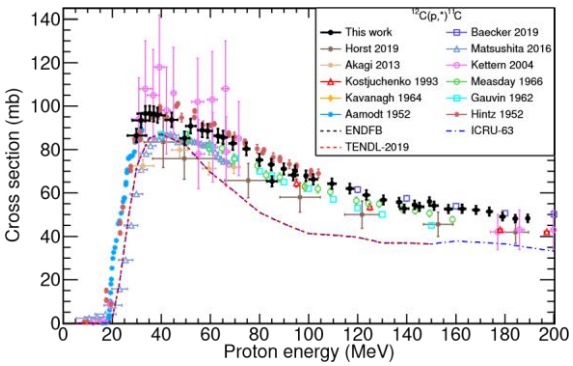

Figure 5. Preliminary production cross section of $^{12}C(p,pn)^{11}C$.

a very good agreement with one of the most recent works, i.e., the experimental data from Bäcker et al. [12].

With this technique, a total of 40 cross section values between 30 and 200 MeV have been obtained. The uncertainty in the cross section values has been calculated taking into account the uncertainty in the PET measurement (3%), the ^{22}Na source (1.5%), the beam current (1%), the foil thickness (1%) and the uncertainty in the fit, obtained with the ROOT software [13] whose algorithms are based on the minimum chi-squared method.

The very good agreement between the overlapped points from two consecutive irradiation energies validates the results and ensures the reproducibility of the measurement.

4 Conclusions and outlook

As a response to the need for more accurate production cross sections of β^+ emitters for PET range verification in proton therapy, this project aims to the measurement of the long-lived isotopes ^{11}C, ^{13}N and ^{15}O in C, N and O. The applied technique provides reliable and accurate measures of the cross sections of interest, measuring several reaction channels in the same experiment, hence minimizing the number of irradiations and systematic errors in the measurement of the activity. The preliminary results of ^{12}C(p,n)^{11}C cross section values is presented, together the available data sets in literature. The good agreement between the data sets obtained by different irradiations constitutes a cross-check for the measurement and technique applied herein. The technique itself has been validate using monitor foils and an IAEA cross section of reference. The preliminary results of ^{12}C(p,n)^{11}C represent then a validation to obtain the cross section of the reaction channels: ^{16}O(p,*)^{11}C, ^{16}O(p,*)^{13}N, ^{16}O(p,*)^{15}O, ^{14}N(p,*)^{11}C, ^{14}N(p,*)^{13}N and ^{14}N(p,*)^{15}O. Further analysis and final results of all reaction channels will be submitted for publication.

This project has received funding from the Spanish Ministry of Economy and Competitiveness projects RYC-2014-15271, FPA2016-77689-C2-1-R and RTI2018-098117-B-C21, from the European H2020-847552 (SANDA) and the V Plan Propio de Investigación Programme from the University of Sevilla. T. Rodriguez-Gonzalez acknowledges the Spanish FPI predoctoral grant.

References

[1] A. C. Knopf and A. Lomax, Physics in Medicine and Biology **58** 131-160 (2013)
[2] H. Paganetti et al., Physics in Medicine and Biology **57** 99-117 (2012)
[3] A. C. Kraan et al., Frontiers in Oncology **5** 150 (2015)
[4] K. Parodi et al., Physics in Medicine and Biology **52** 3369-3387 (2007)
[5] X. Zhu and G. El Fakhri, Theranostics **3,10** 731-40 (2013)
[6] U. Oelfke, G. K. Lam and M. S. Atkins, Physics in Medicine and Biology **41** 177 (1996)
[7] S. España et al., Physics in Medicine and Biology **56** 2687 (2011)
[8] EXFOR data base, https://www-nds.iaea.org/exfor/
[9] T. Rodriguez et al., Radiation Physics and Chemistry **190** 109759 (2022)
[10] Allison et al., Nucl. Instrum. Meth. A **835** 186-225 (2016)
[11] Hermanne et al., Nucl. Data Sheets **148** 338-382 (2018)
[12] C. M. Bäcker et al., Nuclear Inst. and Methods in Physics Research B **440** 75–81 (2019)
[13] CERN, "ROOT. Data Analysis Framework". https://www.root.cern.ch