A method and a target to produce ^{67}Cu

L. Mou[1], P. Martini[1,2], M. Pasquali[1], J. Esposito[1], C. Rossi Alvarez[1], A. Duatti[2] and G. Pupillo[1]

[1]*INFN, Laboratori Nazionali di Legnaro, Legnaro (Padova), Italy;*
[2]*Università di Ferrara e INFN, Sezione di Ferrara, Ferrara, Italy.*

INTRODUCTION

Among the most promising radionuclides for cancer therapy, ^{67}Cu (γ and β^- emitter, $T_{1/2}$=62 h) is worldwide gaining attention of the scientific community thanks to its potential application in theranostics. Indeed, ^{67}Cu is one of the radionuclides intrinsically suitable for both therapeutic and diagnostic purposes and, together with the β^+ emitter ^{64}Cu ($T_{1/2}$=12 h), represents an example of an ideal matched pair for theranostic applications [1]. The case of copper isotopes is of special interest, since ^{64}Cu is useful for PET investigations and dosimetric studies, while ^{67}Cu can be used for SPECT and therapeutic applications [2]. Its combined radiation allows the use of a single radiopharmaceutical (RP), labelled with the same element (^{64}Cu or ^{67}Cu), for both diagnosis and therapy, also permitting dose-tailored treatments. In addition, therapeutic treatments with ^{67}Cu-labelled RPs can be matched with SPECT imaging, allowing the monitoring of the diseased tissue during the therapy, but also permits to follow the pharmacokinetics and the drug efficacy in the long-term. Moreover, copper radioisotopes are presently under the spotlight of the scientific community for their versatile chemistry and biological effectiveness, even as simple Cu^{2+} ions [3]. In fact, it was recently demonstrated that Cu^{2+} ions are selectively up-taken by cancerous cells that, in turn, can be viewed and subsequently destroyed by a cytotoxic radiation dose. These results thus emphasize the enormous potential of ^{67}Cu for nuclear medicine and the urgent need of a reliable supply of this radionuclide.

Currently, the use of ^{67}Cu in preclinical and clinical trials is curtailed by its short availability. ^{67}Cu production still shows considerable challenges. Considering proton-accelerators, the most intensively studied reaction is the $^{68}Zn(p,2p)^{67}Cu$ process. Using this route, at the Paul Scherrer Institute and at the Brookhaven National Laboratories, small amounts of ^{67}Cu are produced [4]. Millicuries amounts of ^{67}Cu are regularly produced at the Oak Ridge National Laboratory, exploiting the $^{68}Zn(p,2p)^{67}Cu$ nuclear reaction and high-energy proton accelerators (200 MeV) [5], and at the Idaho Accelerator Center, based on the $^{68}Zn(\gamma,p)^{67}Cu$ reaction by e-linac [6]. However, worldwide and up to now, there is not a regular supply of ^{67}Cu in sufficient amounts to guarantee clinical trials.

At the INFN-LNL, ^{67}Cu has been a top priority of LARAMED project (LAboratory of RAdionuclides for MEDicine) in the last few years [7]. In 2016, the COME (Copper Measurement) project, funded by CSN3, measured the cross section of the unexplored nuclear reaction $^{70}Zn(p,x)^{67}Cu$ in the energy range 40-70 MeV [8]. Later, the results of COME project have led in 2018 to an INFN patent for an innovative route of ^{67}Cu production [9]. This invention aims at the maximization of the production ratio $^{67}Cu/^{64}Cu$ exploiting 70 MeV proton beams on Zn-70 and Zn-68 target of fixed thickness and in an established configuration.

DESCRIPTION

The object of the invention is to provide an optimized method for the cyclotron production of ^{67}Cu using proton beams in the 70-10 MeV energy range.

By using 70 MeV proton beams and exploiting the nuclear reactions on ^{68}Zn and ^{70}Zn targets (Fig.1), this invention allows to maximize the production of ^{67}Cu and minimize the one of its main contaminant ^{64}Cu.

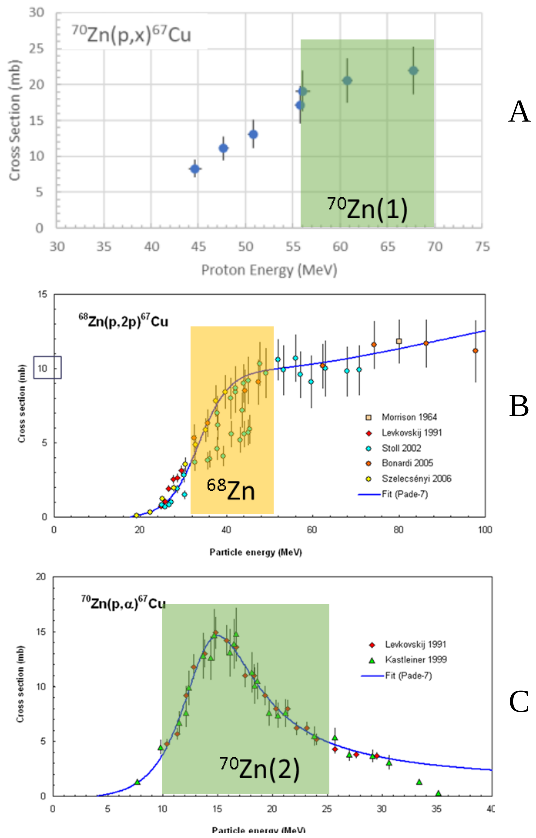

Figure 1: A)Measurement of the $^{70}Zn(p,x)^{67}Cu$ cross section in the 40-70 energy range; B) The IAEA recommended cross section for the $^{68}Zn(p,2p)^{67}Cu$ cross section; C) The IAEA recommended cross section

for the $^{70}Zn(p,\alpha)^{67}Cu$ cross section.

As shown in Fig. 2, the ratio between the production cross sections of ^{67}Cu and ^{64}Cu ($^{67}Cu/^{64}Cu$) is represented for the two different zinc isotopes, specifically ^{70}Zn (black dots and continuous line) and ^{68}Zn (dashed line). To favor the production of ^{67}Cu, it is evident from Fig.2 that it is advantageous to use ^{70}Zn targets for E > 56 MeV, while for lower energies (down to 35 MeV) it is advantageous to use ^{68}Zn targets. The general target configuration, illustrated in Fig. 3 and described in Table 1, is a multi-layers target, comprising a first layer of enriched ^{70}Zn, a second layer of enriched ^{68}Zn, to cover the energy ranges respectively of 70-56 MeV (target of ^{70}Zn) and 56-35 MeV (target of ^{68}Zn). By doing this, the $^{67}Cu/^{64}Cu$ production ratio is maximized regardless of the irradiation times. Moreover, a third layer of enriched ^{70}Zn can be placed after the ^{68}Zn layer, in order to cover the low energy range 25-10 MeV (Fig. 1 C); an additional layer of absorbent material can be interposed in between so that the proton beam reaches this last layer of ^{70}Zn with an energy $E \leq 25$ MeV (Table 1).

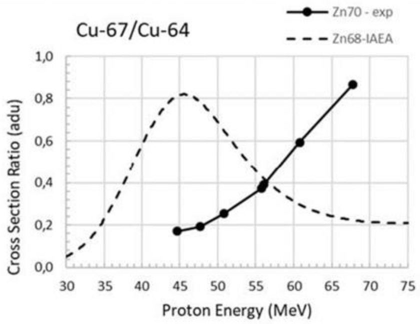

Figure 2: Cu-67/Cu-64 cross section ratio by using 100% enriched target: the Zn-70 case is represented by black dots and a continuous line, the Zn-68 case by a dashed line.

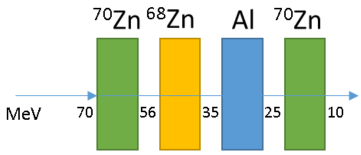

Figure 3: Schematic representation of the target configuration: the Zn-70 layers are reported in green, the Zn-68 layer in yellow and the absorber (aluminum) layer in blue; incoming and outcoming proton beam energies are also reported.

RESULT AND DISCUSSION

Table 1 reports the optimal thicknesses in order to maximize the yield of ^{67}Cu for each energy interval and target layer. A target composed by a first layer of ^{70}Zn and a second layer of ^{68}Zn compared with an equally thick target composed by only ^{68}Zn in the entire range 70-35 MeV, corresponds to an increase of about 46% in the production of ^{67}Cu and a simultaneous decrease of about 12% in the co-production of ^{64}Cu. It should be noted that these estimations have been made considering an irradiation time of 62 hours, corresponding to a saturation factor for ^{67}Cu of 50%.

This double advantage, in view of the use of ^{67}Cu with high radionuclidic purity (RNP), makes it possible to reduce the cooling time aimed at the ^{64}Cu decay; therefore, a further benefit of the method for the production of ^{67}Cu according to the present invention lies in the possibility to obtain greater quantities of ^{67}Cu with high RNP, under the same irradiation conditions, compared to a target entirely composed of ^{68}Zn.

Table 1. Description of the target layers and thicknesses

Strato	*Energia [MeV]*	*Materiale*	*Spessore [mm]*	*Materiale*	*Spessore [mm]*
I°	70-56	^{70}Zn metallico	2,90	^{70}ZnO	3,65
II°	56-35	^{68}Zn metallico	3,40	^{68}ZnO	4,15
Assorbitore (IV°)	35-25	grafite	2,70	alluminio	2,55
III°	25-10	^{70}Zn metallico	1,15	^{70}ZnO	1,45

CONCLUSION

^{67}Cu has been a top priority of LARAMED project in the last years: recent research activities regarding nuclear reaction measurements have led to the INFN patent regarding an optimized target configuration to produce ^{67}Cu. This patent hopefully opens the way of a fruitful collaboration among the SPES/LARAMED reasearch outcomes and the Italian and international industrial network. The experience gained on the technologies for target realization and processing so far is the starting point for developing and optimizing the ^{67}Cu production chain. In the near future we plan to develop the technology necessary to complete the whole procedure for the production of ^{67}Cu. LNL might thus become the first European supplier of this promising radionuclide, promoting the essential research for the development of innovative cancer therapies.

ACKNOWLEDGMENT

Authors would like to thank M. Loriggiola for the realization of enriched ^{70}Zn and ^{63}Cu foils; all the staff of the mechanic's workshop at INFN-LNL; A. Boschi from the University of Ferrara, M. Marengo and G. Cicoria for their support for preliminary tests at S. Orsola Hospital (Bologna); F. Haddad, T. Sounalet and all the staff at the Arronax facility for their constant encouraging help and support during the irradiation runs and experiments. This work is carried out in the context of the Coordinated Research Project (CRP) "*^{67}Cu, ^{186}Re and ^{47}Sc as Emerging Theranostic Radionuclides*" promoted by IAEA [1].

REFERENCES

[1] IAEA (CRP): F22053, (2016), http://cra.iaea.org/cra/explore-crps/all-active-by-programme.html

[2] Qaim S.M. et al. , J. Rad. Nucl. Chem. (2018) 318:1493-1509

[3] Boschi, A. et al., Drug Discov. Today (2018), 23, 1489–1501

[4] Medvedev, D.G. et al.,Appl. Radiat. Isot. (2012), 7, 423–429

[5]NIDC:https://www.isotopes.gov/catalog/product.php?element=Copper&type=rad&rad_product_index=15

[6] Idaho Accelerator Center: http://iac.isu.edu/isotopes.html

[7] Esposito J. et al., Molecules, (2019) 24, 20

[8] Pupillo, G. et al . Annual Report 2017, 130_D_32_D027

[9] Pupillo, G. et al . Patent P2974IT00,INFN, 15 May 2018