Proceedings of the II Symposium on Positron Emission Tomography, Kraków, September 21–24, 2014

Optimization of Cyclotron Production for Radiometal of Zirconium 89

A.M. Dabkowski[a,*], S.J. Paisey[a], M. Talboys[a,b] and C. Marshall[a]

[a]Wales Research and Diagnostic Positron Emission Tomography Imaging Centre (PETIC), School of Medicine, Cardiff University, Heath Park, Cardiff, CF14 4XN, UK

[b]Medical Physics Department, University Hospital of Wales, Heath Park, Cardiff, CF14 4XW, UK

Zirconium 89 (^{89}Zr) is a promising radionuclide for development of new PET agents due to its convenient half life of 78.4 h, β^+ emission rate of 23%, low maximum energy of 0.9 MeV resulting in good spatial resolution, a stable daughter isotope of yttrium-89 (^{89}Y) and favorable imaging characteristics, with only one significant γ-line of 909 keV emitted during decay alongside the 511 keV positron photons. Our aim was to share over 2 years of experience of producing isotopically pure ^{89}Zr via the ^{89}Y(p,n)^{89}Zr nuclear reaction with a COSTIS Solid Target System (STS) and CYCLONE 18/9 cyclotron. We optimized the yields without producing either of the long-lived impurities ^{88}Zr or ^{88}Y. The degradation of the beam energy with 400 and 500 μm thick niobium foils was tested without overheating problems within 2–6 h of irradiation. From repeated measurements of activity, it was clear that there is a bi-exponential decay of radioactivity due to the short lived ^{89m}Zr and ^{89}Zr. The measured half life of the longer lived radionuclide was consistent with value for ^{89}Zr. The energy spectrum from ^{89}Zr had energy peaks at 511 keV and 909 keV and was consistent with ^{89}Zr. Production of ^{89}Zr with 400 ($E_p = 9.8$ MeV) and 500 μm ($E_p = 11.6$ MeV) thick niobium beam degrader was achieved, without producing either ^{88}Zr or ^{88}Y. It was necessary to wait at least 4 hours before measuring the activity and decay correct in order to calculate the ^{89}Zr activity at the end of cyclotron production. Degrading the proton beam to 10 MeV produces radionuclidically pure ^{89}Zr with yields from 8 to 9 MBq/μAh. Whilst this is enough for pre-clinical use, the yield is not enough for either clinical use or commercial supply. Use of thinner beam degraders (400 μm) increases the proton beam energy and increases the radionuclidic yield to 15.5 MBq/μAh whilst maintaining radionuclidic purity.

DOI: 10.12693/APhysPolA.127.1479

PACS: 87.57.uk

1. Introduction

The wide range of biological targeting agents with distribution times of hours and days demands the production of radionuclides with half lives complementary to these biological properties [1] such as the radiometals ^{89}Zr, ^{86}Y and ^{64}Cu.

^{89}Zr is a promising radionuclide for the development of new immuno-PET agents (*in vivo* imaging of cancerous tumours and radioimmunotherapy planning) due to the half life of 78.4 h, stable daughter radionuclide ^{89}Y, β^+ emission rate of 23% and a low maximum energy (0.9 MeV) of emitted positrons delivering a short range in tissue (≈1 mm) and good spatial resolution as a consequence. ^{89}Zr has one significant γ-line (909 keV) emitted during decay and giving low contribution to exposure radiation dose for patient and staff.

In PETIC ^{89}Zr is mainly used for antibody labeling. In this application conjugation of the ^{89}Zr to the antibody can be achieved by binding of the apo chelating group desferrioxamne to a lysine side chain of the antibody using a benzyl-NCS linker (37 °C, pH9, 30 min) [2]. The ^{89}Zr is then mixed with the antibody-chelate conjugate at pH7 and incubated at 37 °C for 60 min. This preparation can be applied to almost any antibody, allowing rapid testing of new biological targets for PET imaging.

*corresponding author; e-mail: dabkowskia@cardiff.ac.uk

There are three nuclear reactions that have been explored for the production of ^{89}Zr: ^{89}Y(p,n)^{89}Zr, ^{89}Y(d,2n)^{89}Zr, ^{nat}Sr(α,xn)^{89}Zr. As PETIC is unable to perform α bombardment, the ^{nat}Sr(α,xn)^{89}Zr reaction is not an option. The CYCLONE 18/9 can accelerate deuterons to 9 MeV. However, this energy is not sufficiently high for the ^{89}Y(d,2n)^{89}Zr reaction [3, 4].

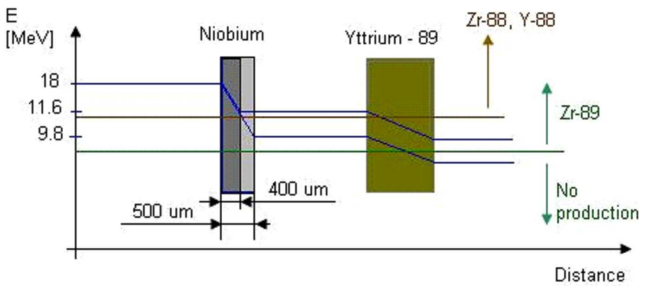

Fig. 1. Schematic picture of the relationship between the Niobium foil thickness and the Zirconium 89 production yield.

Therefore, PETIC decided to investigate the ^{89}Y(p,n)^{89}Zr reaction as the product can be made with high radionuclidic purity at low proton energies (10–11 MeV) [5] easily achieved by the CYCLONE 18/9. Long lived radionuclidic impurities may be generated by the competing nuclear reactions ^{89}Y(p,2n)^{88}Zr (threshold 13.076 MeV) and ^{89}Y(p,pn)^{88}Y (threshold 11.609 MeV). Both of these radioisotopes could significantly increase the radiation dose to the patient if

they were present in the final product. Therefore, both of these production pathways need to be accounted for, and minimised, when producing ^{89}Zr. There is a trade off between the purity of the product and efficiency of the ^{89}Zr cyclotron production (Fig. 1).

The proton beam of CYCLONE 18/9 cyclotron had to be degraded from 18 MeV to l0–11 MeV by the niobium window foil installed in the COSTIS STS [6].

Our aim was to prove that usable yields of isotopically pure ^{89}Zr could be produced in an IBA CYCLONE 18/9 cyclotron equipped with a COSTIS STS and a niobium beam degrader without producing either ^{88}Zr or ^{88}Y.

2. Experimental

2.1. Solid target design and preparation

The target material ^{89}Y was obtained as a 150 μm thick foil with isotopic purity of 99.9% from Goodfellow Cambridge Ltd (Fig. 2 — centred).

The solid target holder used in PETIC was based on the design described by Walther et al. [7] (Fig. 3).

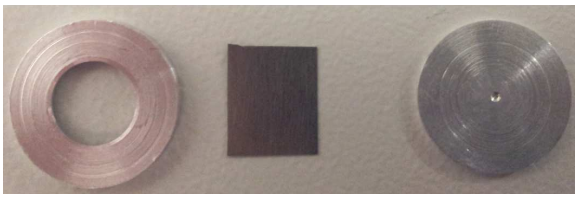

Fig. 2. Aluminum solid target holder with ^{89}Y target foil shown in the center.

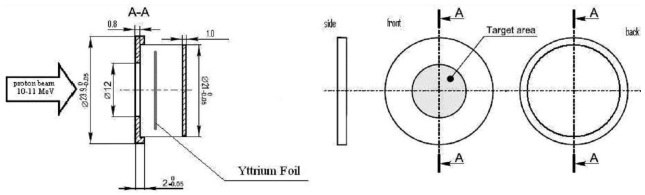

Fig. 3. Solid target "coin" design — aluminum 2-pieces holder and yttrium foil inside.

2.2. Beam energy degradation

The proton beam of CYCLONE 18/9 cyclotron was degraded from 18 MeV to $\approx$ 9.8 MeV using a 500 μm thick niobium foil and to $\approx$ 11.6 MeV using a 400 μm thick niobium foil (Fig. 4) (Goodfellow Cambridge Ltd). The energy degradation foil was installed in the COSTIS STS as a vacuum window.

2.3. Post production measurements

The COSTIS STS is equipped with a conveyor belt (FlexLink) providing safe transportation of solid targets from the vault (Fig. 5). After irradiation, the coin is released and dropped into an open transport shuttle and waits for a signal from the COSTIS STS to start delivery. Both COSTIS STS and conveyor belt are operated by panels located outside the vault. The automatic closing mechanism was removed from the vault and located on

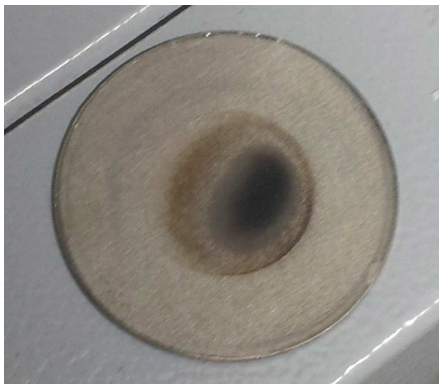

Fig. 4. Used niobium vacuum window for the protons beam energy degradation (note the dark spot — beam trace).

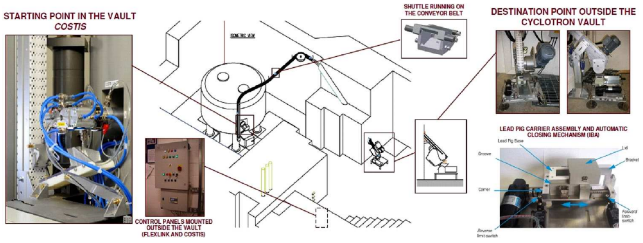

Fig. 5. Schematic view of the solid target disc transportation system.

the other end of conveyor belt. Coins are delivered in lead pigs using the lift from cyclotron suite located one level under the lab. The hot cell has its own loading system (independent of the main hot cell door) with a drawer and hoist for automatic lead pig opening and delivery of radioactive coin. The coin is opened and yttrium foil released for further processing using in house equipment.

The activity of the ^{89}Zr produced was measured using a CRC 25R CAPINTEC Dose Calibrator set to a dial factor of 490 at least 4 h after the end of beam, to allow for the decay of short lived ^{89m}Zr which is also produced alongside ^{89}Zr, and decay corrected to end of beam (EOB). Capintec CRC-25PET dose calibrators does not have a published calibration factor for ^{89}Zr but a suitable calibration factor was determined through cross-calibration with a CRC-15R dose calibrator (which has a published calibration factor for ^{89}Zr (465) [8]. Long lived impurities were assessed using an EG & G Ortec (NaI and HPGe) detectors with Canberra multi channel analysers.

3. Results and discussion

The degradation of the beam energy with 400 and 500 μm thick niobium foils were achieved without overheating problems with long irradiation times (2–6 h).

From repeated measurements of activity (Fig. 6), it is clear that there is a bi-exponential decay of radioactivity due to the short lived ^{89m}Zr and ^{89}Zr. The measured half life of the longer lived radionuclide was 78.841 h which is consistent with ^{89}Zr.

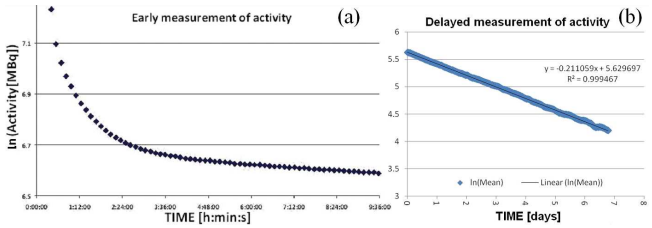

Fig. 6. Early (a) and delayed (b) measurements of activity from ^{89}Zr production with 0.5 mm thick niobium beam degrader showing that good base for ^{89g}Zr activity extrapolation constitute delayed measurements after 4 h from EOB.

TABLE I

Zirconium 89 and its impurities' half lives expected spectral characteristics.

Expected energy spectrum for:		
^{89}Zr	^{88}Zr	^{88}Y
78.41 h	83.4 d	106.6 d
511 keV 23%	393 keV 97%	511 keV 20%
909 keV 99%		1836 keV 99%
1713 keV 0.8%		898 keV 94%
1745 keV 0.1%		2734 keV 0.7%
1657 keV 0.1%		851 keV 0.1%

Production of ^{89}Zr with 500 μm thick niobium beam degrader ($E_p = 9.8$ MeV) was achieved, without producing either ^{88}Zr or ^{88}Y (Fig. 7) and resulted in yields of 8 to 9 MBq/μAh.

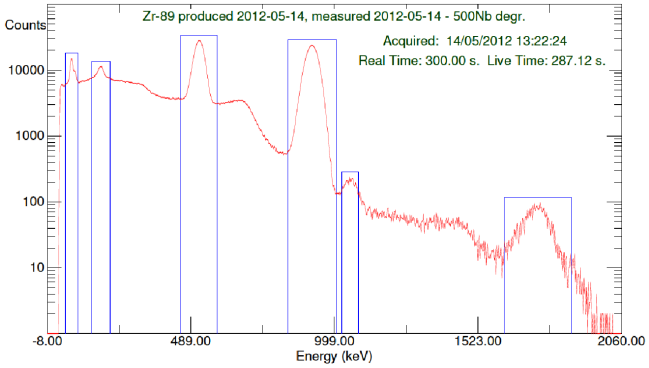

Fig. 7. Energy spectrum from ^{89}Zr production with 0.5 mm thick niobium beam degrader shows the characteristic 511 and 909 keV gamma emissions from ^{89}Zr.

The energy spectrum from ^{89}Zr produced using niobium foil thickness of 400 μm (Fig. 8) has energy peaks at 511 keV and 909 keV and is consistent with ^{89}Zr, too.

Production of ^{89}Zr with 400 μm thick niobium foil (E_p = 11.6 MeV) results in a higher yield (14–16 MBq/μAh) without producing evidence of ^{88}Zr or ^{88}Y impurities on spectra measured 2 months after EOB (Fig. 8). More accurate measurements with a HPGe detector show (Fig. 9) that, beside the characteristic 511,

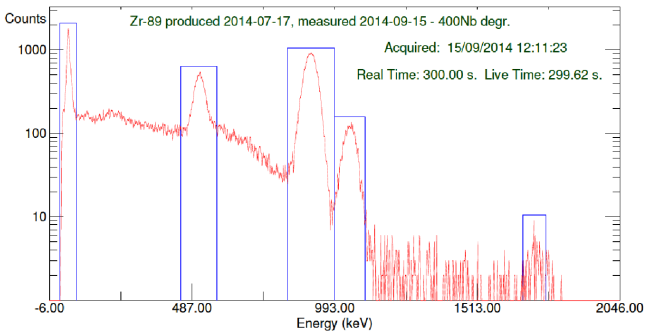

Fig. 8. Energy spectrum from ^{89}Zr production with 0.4 mm thick niobium beam degrader measured 2 months after EOB also shows mainly the characteristic 511 and 909 keV gamma emissions from ^{89}Zr.

909 keV gamma emissions and possible summation or Compton scatter peaks, only a very minor emissions from ^{89}Zr (Table I) are present around 1.7 MeV energy value.

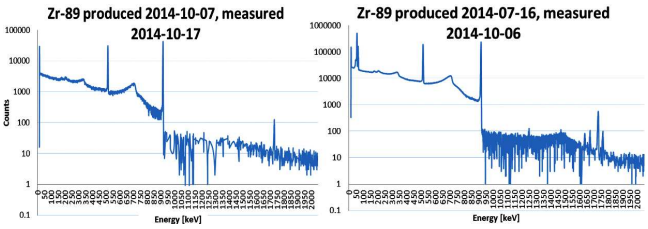

Fig. 9. Energy spectra for ^{89}Zr production with 0.4 mm thick Niobium beam degrader measured with HPGe detector show the characteristic 511 and 909 keV gamma emissions from ^{89}Zr and some minor peaks around 1.7 MeV energy value what is fully consistent with Tab. I values for ^{89}Zr.

Comparison of these results is consistent with values reported in the literature [7]. However, from the summary of the production yields for ^{89}Zr presented by Taghlio et al. [9], it is obvious that our yield is not as high as published by some other authors [3, 9, 10]. There is still scope to increase our yield by varying parameters such as increasing the energy for beam protons, changing the method of target preparation or altering the target thickness or changing the beam degradation. However, we have achieved our principle aim of proving that it is possible to produce an isotopically pure ^{89}Zr with a typical low energy cyclotron configuration.

4. Conclusions

The production of pure ^{89}Zr with a CYCLONE 18/9 and COSTIS STS is possible. It is necessary to wait at least 4 h before measuring the activity in order to calculate the ^{89}Zr activity at the end of cyclotron production. Degrading the proton beam to 10 MeV produces radionuclidically pure ^{89}Zr with yields from 8 to 9 MBq/μAh. Whilst this is enough for pre-clinical use, the yield is

not enough for either clinical use or commercial supply. Using thinner beam degraders to increase the proton beam energy increases the radionuclidic yield up to 15.5 MBq/μAh without the presence of radionuclidic impurities. Further improvement of the yield is planned as the value is not very high comparing to the other literature examples [9]. However reduction of impurities might be a challenge.

TABLE II

Zirconium 89 productions parameters and yields.

Beam time [h]	Beam current [uA]	Niobium thickness [μm]	Beam energy [MeV]	^{89g}Zr activity EOB [MBq]	Average yield of the ^{89}Y(p,n)^{89}Zr nuclear reaction [MBq/uAh]
3	20	500	9.8	529.5	8.83
3	30	500	9.8	791.7	8.79
2.1	30	400	11.6	973.4	15.45
1.5	20	400	11.6	445	14.83
3	30	400	11.6	1400	15.56
3.5	30	400	11.6	1398	13.31
6.28	25	400	11.6	2364	15.06

Acknowledgments

Many thanks to FlexLink, IBA (technical support), ELEX Commerce, Stephan Preusche (valuable information and advice) and Paul Rabaiotti.

References

[1] T.J. Wadas, E.H. Wong, G.R. Weisman, C.J. Anderson, *Chem. Rev.* **110**, 2858 (2010).

[2] M.J. Vosjan, L.R. Perk, G.W.M. Visser, M. Budde, P. Jurek, G.E. Kiefer, G.A.M.S van Dongen, *Nature Protocol* **5**, 739 (2010).

[3] M.S. Uddin, M. Hagiwara, M. Baba, F. Tarkanyi, F. Ditroi, *Appl. Radiat. Isot.* **63**, 367 (2005).

[4] J. Zweit, S. Downey, H.L. Sharma, *Appl. Radiat. Isot.* **42**, 199 (1991).

[5] M.A. Avila-Rodriguez, J. Rajander, J.O. Lill, K. Gagnon, J. Schlesinger, J.S. Wilson, S.A. McQuarrie, O. Solin, *Nucl. Instrum. Methods Phys. Res. B* **267**, 1867 (2009).

[6] COSTIS — Operating Manual, TS04-80.00.00.01, Elex Commerce, 2007.

[7] M. Walther, P. Gebhardt, P. Grosse-Gehling, L. Würbach, I. Irmler, S. Preusche, M. Khalid, T. Opfermann, T. Kamradt, J. Steinbach, H.P. Saluz, *Appl. Rad. Isotopes* **69**, 852 (2011).

[8] J.P. Holland, Y. Sheh, J.S. Lewis, *Nucl. Med. Biol.* **36**, 729 (2009).

[9] M. Taghilo, T. Kakavand, S. Rajabifar, P. Sarabadani, *Int. J. Phys. Sci.* **7**, 1321 (2012).

[11] S.A. Kandil, B. Scholten, Z.A. Saleh, A.M. Youssef, S.M. Qaim, H.H. Coenen, *J. Radioanal. Nucl. Chem.* **274**, 45 (2007).