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Spot-welding solid targets for high current cyclotron irradiation

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Abstract

Zirconium-89 finds broad application for use in positron emission tomography. Its cyclotron production has been limited by the heat transfer from yttrium targets at high beam currents. A spot welding technique allows a three-fold increase in beam current, without affecting ⁸⁹Zr quality. An yttrium foil, welded to a jet-cooled tantalum support base accommodates a 50 μ A proton beam degraded to 14 MeV. The resulting activity yield of 48 ± 4 MBq/(μ A·hr) now extends the outreach of ⁸⁹Zr for a broader distribution.

Keywords

Zirconium-89; ⁸⁹Zr; Zr-89; Ti-44; spot welding; cyclotron solid targetry

I. Introduction

There has been an increasing acceptance of the radiometals of the 3-d and 4-d subshells to label positron emission tomography (PET) tracers with protracted clearance rates. Peptides, monoclonal antibodies, nanostructures and a host of large molecules can target specific cellular receptors to signal disease, but require a radiolabel with both chemical versatility and a half-life of the order of hours to days to match the slow uptake kinetics often found in various tumors [Anderson and Welch, 1999]. The cyclotron production of scores-of-GBq-levels of the conventional positron emitters (¹¹C and ¹⁸F) involve the proton irradiation of gaseous N₂ or liquid H₂¹⁸O. This target science is well developed, while the seemingly simpler prospect of high current bombardment of solid target substrates remains challenging.

Zirconium-89 ($t_{1/2}=78.4$ h) is the most thoroughly clinically developed positron emitting radiometal nuclide with its incorporation into 11 United States clinical trials as of 2016 (clinicaltrials.gov). Its production in moderate (100s of MBq) quantities through the ⁸⁹Y(p,n)⁸⁹Zr nuclear reaction (Saha et al., 1966) is currently feasible using small medical cyclotrons capable of irradiating yttrium targets with 5 – 20 μ A of 10 – 20 MeV

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protons. A variety of cyclotron targetry methods have been investigated including the irradiation of Y foils (Link et al., 1986 and DeJesus and Nickles, 1990), Y-sputtered copper (Meijs et al., 1994), powdered Y (Nagatsu et al., 2012), sedimented Y_2O_3 (Sadeghi et al., 2010), and aqueous solutions of $Y(NO_3)_3$ (Pandey et al., 2016). However, as clinical trials requiring 40 – 200 MBq per human dose of ^{89}Zr -labeled compound continue to expand, the need for methods of producing GBq quantities of ^{89}Zr is increasing. Modern small medical cyclotrons are currently capable of routinely accelerating 100+ μA of protons. As a result, the main factor limiting ^{89}Zr production is in the design of Y targets that can withstand the hundreds to thousands of watts of thermal power deposited by such a proton beam. In recent years, target designs capable of withstanding 30 – 45 μA of proton irradiation of water- and He-cooled Y foils have been demonstrated by Dabkowskia et al. (2015), Ciarmatori et al. (2011), and Siikanen et al. (2014). However, the former two of these methods utilize thin (0.15 mm) ^{89}Y target foils limiting the overall ^{89}Zr production capacity. On the contrary, Siikanen et al. (2014) utilize a high mass (~3g) ^{89}Y target, which would limit the specific activity and therefore radiopharmaceutical utility of the produced ^{89}Zr .

At the University of Wisconsin, ^{89}Zr is routinely produced by clamping a $1\text{ cm}^2 \times 0.64\text{ mm}$ thick yttrium foil to a direct water-jet cooled 1.9-cm diameter, 0.5-mm-thick Ag disc. This 300 mg target accepts the PETtrace proton beam, degraded from 16 MeV down to 14 MeV by a 0.125 mm foil of molybdenum upstream. At this lower entrance energy, the $^{89}Y(p,n)$ reaction was avoided, which would lead to the objectionable long-lived ^{88}Zr and ^{88}Y contaminants. Furthermore, the 0.64 mm yttrium thickness corresponds to an energy loss of about 7 MeV, capturing most of the (p,n) cross section while minimizing the mass of yttrium entering into the radiochemical separation steps. While these irradiation conditions resulted in a favorable ~40 MBq/($\mu A \cdot hr$) yield of ^{89}Zr , the Y foil cooling was provided only indirectly by conduction through the water jet cooled silver disk substrate and the aluminum target support. Thus, the maximum beam tolerated by this clamped yttrium foil was found to be 15 μA , at which the post-irradiation Y foil appeared noticeably blackened in the beam strike. When irradiated with 20 μA protons, the Y foil began to visibly melt, sputter, and pit in the beam strike, reducing overall ^{89}Zr production yield. It was the goal of this work to improve the cooling of the Y target foil to allow for higher intensity proton irradiations. Accomplishing this would allow for a significant increase in the production capacity of ^{89}Zr and a considerable decrease in the number of hours per week dedicated to its production.

Several factors were considered with the target redesign. The heat transfer limit suggests direct water-cooling of the Y foil, but this risks chemical attack with unwanted cations entering the cooling water, as well as cooling water impurities potentially depositing on the foil. Similarly, slanting the target relative to the beam reduces the areal power density, but increases the mass of yttrium entering the separation phase. Thus, we chose to explore spot welding the yttrium foil to a suitable target bed, capable of being directly cooled with the standard water jet technique at normal incidence. This target support material needs to be

- refractory, yet a good thermal conductor
- resistant to the deionized water stream of the cyclotron cooling system,

- and, following irradiation, resistant to the 6 M HCl acid dissolution step in the Zr/Y separation.

The present work aims to show that spot welding yttrium target material to a water-jet-cooled inert target backing allows for significant gains in the production capacity of ^{89}Zr . The detailed methods and results show this targetry method to be a simple, robust method for high current cyclotron irradiations of yttrium and shows promise for its more broad applicability to the production of other low production yield radionuclides.

II. Materials and methods

Unless otherwise stated, reagents were obtained from commercial vendors and used as received. Post irradiation chemical processing of targets was performed using ultra pure 18 M Ω water and Optima grade chemicals (Fisher Scientific) to minimize trace metal contamination.

The irradiation targets investigated in this work were composed of yttrium, which like most odd-Z elements, is mono-isotopic, allowing for the use of foils of high purity (99.9%) of natural isotopic abundance (Alfa Aesar). Cyclotron targets were composed of a layer yttrium (0.64-mm-thick) spot welded to an inert tantalum disc (0.5 mm thick) using a resistance spot welder (White Dog, CHIFW040) fitted with copper or silver electrodes, shown in Figure 1. The welded target disc was then clamped to a water-jet-cooled target support fixture with two 2–3-mm-thick, 12.7-mm-inner-diameter aluminum clamp rings with a 0.125-mm-thick molybdenum or tantalum foil for proton energy degradation, shown in Figure 2. The rear surface of the target disc that forms an O-ring seal separating the cyclotron vacuum from the water jet cooling was leak-tested with a simple static pressure test device. A bicycle pump, check-valved and read out with a high resolution pressure transducer, pressurized the assembled target water trace to 0.6 MPa to detect any potential leaks. Proton irradiation of the target fixture with 16.0 MeV protons was monitored for prompt neutron and gamma dose rates to detect any target deterioration in real time (Barnhart, et al., 2012).

After irradiation, the 4-minute $^{89\text{m}}\text{Zr}$ was allowed to decay before disassembly and assay of the ^{89}Zr ground state activity with a radioactivity dose calibrator (Capintec CRC-Dual PET, 489 calibration constant) and an efficiency-calibrated high purity germanium gamma detector (at 909 keV). The ^{89}Zr was isolated from the target disc in a procedure adapted from Holland et al. (2009). Briefly, the yttrium was selectively dissolved in 5 mL of 6 M HCl, leaving the Ta backing disc intact. The dissolved solution was then diluted with 10 mL of H_2O and passed through a column of ~50 mg of in-house-prepared hydroxamate-functionalized silica resin, trapping ^{89}Zr . The resin was subsequently rinsed with 10 mL of 2 M HCl, 10 mL of H_2O and the ^{89}Zr eluted with 1 mL of 1 M oxalic acid (Aldrich Chemicals, 99.999% trace metals basis) in four 100 – 500 μL aliquots. The final ^{89}Zr product was assayed for desferoxamine (DFO) effective specific activity (ESA) according to literature procedures with the Zr chelation yield determined through autoradiography-visualized silica thin-layer chromatography with 0.05 M diethylenetriaminepentaacetic acid (DTPA) mobile phase (Holland et al., 2009) or cellulose chromatography with 2:1:1::n-butanol: H_2O :acetic acid mobile phase (Meijs et al., 1992).

III. Results

A. Pre-irradiation

The process of spot welding involves the joining of two metallic surfaces by pinching between electrodes, applying a high power electric current causing localized resistive heating and cleavage of the two surfaces. Thus, for successful spot welding, the proper substrate must be well paired with the target foil in several material and metallurgical properties, including melting point, electrical resistivity, and binary alloy phase behavior. Particularly, it was found that the backing material must have a significantly higher melting point than the target foil to maintain integrity during the welding process. Thus, 0.64-mm-thick yttrium (melting point = 1522 °C; $\rho = 60 \mu\Omega\cdot\text{cm}$) was successfully welded to 0.25 – 0.5 mm tantalum (3017 °C; $13 \mu\Omega\cdot\text{cm}$), molybdenum (2623 °C; $53.4 \mu\Omega\cdot\text{cm}$), tungsten (3422 °C; $5.3 \mu\Omega\cdot\text{cm}$), and niobium (2477 °C; $15 \mu\Omega\cdot\text{cm}$), while less refractory substrates such as silver (962 °C; $1.6 \mu\Omega\cdot\text{cm}$) and aluminum (660 °C; $2.6 \mu\Omega\cdot\text{cm}$) were unsatisfactory. Examination of the binary alloy phase behaviors of Y-Ta, Y-Mo, Y-W, and Y-Nb as compiled by Elliot (1965) yields a common feature that all show a small degree of miscibility (<0.5 to 10 atom percent Ta/Mo/W/Nb) in liquid Y with a drop in melting temperature observed for the alloys. Thus, the spot welding mechanism for Y to these refractory metals likely involves the heating of Y above its melting point, at which a small amount of refractory substrate metal dissolves, forming an interfacial binary alloy and intimately binding the two materials. Additional target foils were investigated to probe the versatility of the spot welding technique, including the successful spot welding of scandium (1541 °C; $56 \mu\Omega\cdot\text{cm}$) to Ta for the potential cyclotron production of $^{44,45}\text{Ti}$, and holmium (1474 °C; $81 \mu\Omega\cdot\text{cm}$) to Ta in argon atmosphere for the potential production of ^{165}Er . Following successful spot welding, the resulting surfaces were somewhat blackened, which was removed by polishing with a Dremel rotary brush.

In test welds using copper welding electrodes, discoloration of the yttrium foil at the weld spot led to the hypothesis that small deposits of the copper electrode material were fused into the yttrium surface. While copper could be dissolved in 6 M HCl and potentially enter the ^{89}Zr chemical isolation procedure, two studies implied the innocuous nature of this potential contaminant. First, ^{63}Zn or ^{65}Zn would be the activation products from the irradiation of any copper residue. No such activity was seen after irradiation of spot-welded Y/Ta targets or the subsequently extracted ^{89}Zr . Secondly, performing the ^{89}Zr chemical isolation procedure using tracer ^{64}Cu in HCl resulted in no detectable (<0.03% of loaded) ^{64}Cu extracting onto the hydroxamate resin or eluting with the ^{89}Zr oxalate.

Nonetheless, the top spot welder electrode, that contacts the yttrium facing the proton beam, was replaced with a silver electrode shown in Figure 1. Furthermore, the input voltage of the spot welder was reduced to 80 VAC to provide more controlled welds, balancing between weld spots obtained at 120 VAC exhibiting a significantly cratered or perforated Y foil and weld spots obtained at 20 – 60 VAC that did not sufficiently bond the Y and Ta. The tantalum support thickness of 0.5 mm proved to be ideal for bonding both yttrium and scandium. Roughly twenty individual spot welds uniformly cover the 1 cm^2 yttrium target, performed in less than five minutes. At 50 μA of 16 MeV protons, the thermal impedance

added by this tantalum foil would result in a 100° C temperature difference between the beam strike and the rear, water-cooled surface.

B. Irradiation

The water-jet-cooled Ta-welded Y target and Mo/Ta degrader assembly shown in Figure 2 was irradiated with successively intense proton beams: 20, 30, 40, and 50 μA for 1 – 2 hours. Both gamma and neutron flux scaled linearly with beam current, with “blank” targets of a water-jet-cooled Ta target and Ta degrader assembly producing roughly half of the measured flux. The tantalum degrader assembly had advantages over the molybdenum degrader as it reduced the neutron and gamma background during bombardment as well as mitigated the potential introduction of sputtered molybdenum onto the yttrium target face. Additionally, water-jet-cooled Ta-welded Sc and Ta-welded Ho target assemblies (with no degrader) were challenged with a 50 μA irradiation for several hours to test robustness of Sc-Ta and Ho-Ta welded targets for the potential production of $^{44/45}\text{Ti}$ and ^{165}Er , respectively.

C. Post-irradiation

Test irradiations of Y foils welded to Ta with a small number (< 5) weld spots or with spot welds performed at too low of a welding voltage demonstrated the major mechanism of target failure. In these cases irradiated with 20 – 45 μA protons, post-irradiation visual inspection revealed a portion of the Y foil that released from the Ta substrate and began to show signs of melting and sputtering of the Y target material. These target failures were successfully mitigated by increasing the spot welding voltage and stippling 20 – 30 weld spots across the entire foil. Such a Ta-welded Y target is shown in Figure 3, before and after irradiation with 50 μA protons for 1 hour. The beam strike is evident, but no significant yttrium mass loss was observed. The amount of discoloration to the Y target foil was similar to that of a 15 μA irradiation of Y foil using the previously used ^{89}Zr production methods described in section I. This irradiation current is also significantly higher than that of Dabkowskia et al. (2015) and Ciarmatori et al. (2011) used to irradiate thin Y foils and slightly higher than the 45 μA that Siikanen et al. (2014) used to irradiate large direct H_2O -cooled Y foils. Irradiation of Ta-welded Sc and Ta-welded Ho targets with 50 μA protons for 1 – 3 hours yielded visual inspection results identical to that of Ta-welded Y with only slight discoloration and no visible target foil damage observed.

End of bombardment (EOB) ^{89}Zr production yields of $48 \pm 4 \text{ MBq}/(\mu\text{A}\cdot\text{hr})$ were consistent regardless of irradiation current and in good agreement with those observed with our previously used methods described in section I. Additionally, this yield is in agreement with the $49 \pm 4 \text{ MBq}/(\mu\text{A}\cdot\text{hr})$ measured by Siikanen et al. (2014) and significantly higher than that observed by Dabkowskia et al. (2015) and Ciarmatori et al. (2011) irradiating thinner Y foils at lower proton energies. Thus, the significantly improved proton beam current durability of the Ta-welded Y target increased ^{89}Zr production capacity by more than threefold.

The dissolution and radiochemical isolation of ^{89}Zr proceeded in good agreement with previous experience with irradiated Y foils, with ~90% radiochemical yield of ^{89}Zr in the oxalic acid elute. Tantalum backing substrate showed no degradation during the dissolution

of Y target material. The resilience of the Ta substrate toward hydrochloric acid was further investigated by immersing Ta in 12 M HCl for 12 days, with no visible change or measurable mass loss observed. The EOB DFO ESA measured for ^{89}Zr oxalate was 60 ± 70 GBq/ μmol ($n = 10$). This is in agreement with our EoB DFO ESA results for ^{89}Zr produced through previous methods of 60 ± 50 GBq/ μmol ($n = 124$). Additionally, these results are in agreement with EOB DFO ESA values of 17 – 44 GBq/ μmole reported by Holland et al. (2009) and those of 4 ± 4 GBq/ μmole reported by Wooten et al. (2013). It is possible that the higher run-to-run variability in ESA values measured in the current work is as a result of the spot welding method potentially resulting in higher trace metal contamination of the ^{89}Zr through the presence of the cooling-water-contacted Ta backing, high-proton-current sputtered degrader foil material, or from the welding electrode. However, the fact that the average specific activity is as good or better than all previously reported methods leads to the conclusion that no significant impurities are added to the final ^{89}Zr product in the spot welding process. Future studies involving microwave plasma atomic emission spectroscopy will investigate this further. Radiolabeling of a DFO-conjugated monoclonal antibody with Ta-welded-Y-produced ^{89}Zr proceeded with typical radiochemical labeling yields. Table 1 summarizes ^{89}Zr production results obtained with Ta-welded Y targets and those recently published in literature.

IV. Conclusions

Welding target foils to a cooled tantalum support has allowed us to more than triple the beam current during irradiation of yttrium, resulting in a significant increase in ^{89}Zr production capacity and a decrease in the amount of cyclotron time per week required for its production. The spot welding method has been shown to effectively bond other brittle metals, such as scandium and holmium, to refractory metal substrates, highlighting the versatility of the method for the production of other high proton current cyclotron targets. Zirconium-89 was isolated from Ta-spot-welded Y foil using routine methods and the final ^{89}Zr product was found to react well in chelator-based radiolabeling procedures.

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Highlights

- Previous methods of ^{89}Zr production limit proton irradiation currents to 15 μA .
- A high current proton irradiation target made by spot welding Y to a Ta base.
- Ta-welded Y target resilient toward 50 μA , 14 MeV proton irradiations.
- Target yields ^{89}Zr at a rate of $48 \pm 4 \text{ MBq}/(\mu\text{A}\cdot\text{hr})$.
- No significant difference in resulting ^{89}Zr specific activity.

Figure 1.
Photograph of spot welding 0.64 mm thick Y to 0.5 mm thick Ta.

Figure 2.
Schematic of direct-jet-cooled Ta-welded Y target assembly with beam energy degrader foil.

Figure 3. Photographs of Ta-welded Y target (a) before irradiation, (b) after 2 hour 50μA proton irradiation.

Table 1Comparison of ^{89}Zr cyclotron production results with literature.

Max. proton current (μA)	^{89}Zr yield ($\text{MBq}/(\mu\text{A}\cdot\text{hr})$)	DFO ESA ($\text{GBq}/\mu\text{mol}$)	Reference
50	48 ± 4	60 ± 70	This work
45	49 ± 4	n/a	Siikanen et al. (2014)
30	14 – 16	n/a	Dabkowskia et al. (2015)
35	21 ± 2	n/a	Ciarmatori et al. (2011)
15	56 ± 4	17 – 44	Holland et al. (2009)
15	34 ± 6	4 ± 4	Wooten et al. (2013)