Improved Production and Processing of ^{89}Zr using a Solution Target

Mukesh K. Pandey^{1,*}, Aditya Bansal¹, Hendrik P. Engelbrecht¹, John F. Byrne², Alan B. Packard³, Timothy R. DeGrado^{1,*}

¹Department of Radiology, Mayo Clinic Rochester MN 55905

²Division of Nuclear Medicine, Brigham and Women's Hospital, Harvard Medical School Boston MA 02115

³Division of Nuclear Medicine and Molecular Imaging, Boston Children's Hospital, Harvard Medical School Boston MA 02115

***Corresponding Authors**

Dr. Mukesh K Pandey

Email: pandey.mukesh@mayo.edu. Phone: (507) 538-4221. Fax: (507) 266-4461

Professor Timothy R DeGrado

Email: degrado.timothy@mayo.edu, Phone: (507) 538-4319. Fax: (507) 266-4461

Abstract

Objective: The objectives of the present work were to improve the cyclotron production yield of ^{89}Zr using a solution target, develop a practical synthesis of the hydroxamate resin used to process the target, and develop a biocompatible medium for ^{89}Zr elution from the hydroxamate resin.

Methods: A new solution target (BMLT-2) with enhanced heat dissipation capabilities was designed by using helium-cooled dual foils (0.2 mm Al and 25 μ Havar) and an enhanced water-cooled, elongated solution cavity in the target insert. Irradiations were performed with 14 MeV protons on a 2 M solution of yttrium nitrate in 1.25 M nitric acid at 40- μ A beam current for 2 h in a closed system. Zirconium-89 was separated from Y by use of a hydroxamate resin. A one-pot synthesis of hydroxamate resin was accomplished by activating the carboxylate groups on a carboxymethyl cation exchange resin using methyl chloroformate followed by reaction with hydroxylamine hydrochloride. After trapping of ^{89}Zr on hydroxamate resin and rinsing the resin with HCl and water to release Y, ^{89}Zr was eluted with 1.2 M $\text{K}_2\text{HPO}_4/\text{KH}_2\text{PO}_4$ buffer (pH 3.5). ICP-MS was used to measure metal contaminants in the final ^{89}Zr solution.

Results: The BMLT-2 target produced 349 ± 49 MBq (9.4 ± 1.2 mCi) of ^{89}Zr at the end of irradiation with a specific activity of 1.18 ± 0.79 GBq/ μ g. The hydroxamate resin prepared using the new synthesis method showed a trapping efficiency of 93% with a 75 mg resin bed and 96-97% with a 100-120 mg resin bed. The elution efficiency of ^{89}Zr with 1.2 M $\text{K}_2\text{HPO}_4/\text{KH}_2\text{PO}_4$ solution was found to be $91.7\pm 3.7\%$, compared to $>95\%$ for 1 M oxalic acid. Elution with phosphate buffer gave very small levels of metal contaminants: Al = 0.40-0.86 μ g (n= 2), Fe = 1.22 ± 0.71 μ g (n= 3), Y = 0.29 μ g (n= 1).

Conclusions: The BMLT-2 target allowed doubling of the beam current for production of ^{89}Zr , resulting in a greater than 2-fold increase in production yield in comparison with a conventional liquid target. The new one-pot synthesis of hydroxamate resin provides a simpler synthesis method for the ^{89}Zr trapping resin. Finally, phosphate buffer elutes the ^{89}Zr from the hydroxamate resin in high efficiency while at the same time providing a more biocompatible medium for subsequent use of ^{89}Zr .

Key words: ^{89}Zr , cyclotron targetry, solution target, hydroxamate resin

1. Introduction

Zirconium-89 has gained considerable attention for labeling antibodies due to its favorable PET imaging characteristics (β^+_{max} - 0.9 MeV, 22.7%) and a half-life ($T_{1/2}$ - 78.4 h) that matches the biological half-life of antibodies. Several monoclonal antibodies have been labeled with ^{89}Zr using the bifunctional chelator desferrioxamine (DFO) and are currently under clinical investigation for diagnostic imaging and therapeutic monitoring applications. For example, ^{89}Zr -DFO-cetuximab is an anti-epidermal growth factor receptor monoclonal antibody labeled with ^{89}Zr that is being investigated for PET imaging of metastatic colorectal cancer [1], while ^{89}Zr -DFO-bevacizumab is an anti-vascular endothelial growth factor-A monoclonal antibody labeled with ^{89}Zr that is being investigated for evaluation of lesions in patients with Von Hippel-Lindau disease [2], renal cell carcinoma [3], breast cancer [4], and neuroendocrine tumors [5]. Zirconium-89-DFO-trastuzumab is a radiolabeled anti-HER2 monoclonal antibody currently under investigation for breast cancer imaging [6]. Various other monoclonal antibodies are being investigated for PET imaging of pancreatic, ovarian and prostate cancers [7]. Zirconium-89 has also been investigated for cell labeling using ^{89}Zr -protamine sulfate [8], ^{89}Zr -oxine [9, 10], and ^{89}Zr -desferrioxamine-NCS ($^{89}\text{ZrDBN}$ [11]. The 78.4 h half-life of ^{89}Zr allows *in-vivo* tracking of the labeled cells for prolonged periods of time (weeks), which is being instrumental in understanding the cell-based therapies and imaging.

Zirconium-89 can be produced using solid and liquid target methods via the $^{89}\text{Y}(p,n)^{89}\text{Zr}$ reaction [12-14]. Solid target methods require higher infrastructure cost because of the expense of the target handling system and are challenging to implement in PET facilities equipped with self-shielded cyclotrons. However, the solution target approach offers a viable alternative to the solid target system that can meet the modest needs for ^{89}Zr at most institutions.

Production of radiometals in a solution target is challenging because of in-target salt precipitation and unstable target pressures caused by gas evolution during irradiation [14], but these problems have been attenuated by using nitrate salts of the target metal in dilute nitric acid solutions [14]. We reported a mechanistic study on the effect of solution composition on in-target chemistry [14], the effect of nitric acid [14], and a second-generation solution target (Brigham Mayo Liquid Target-2 or BMLT-2) design that enhances heat dissipation during production of ^{68}Ga [15]. In the present study, we investigated the use of

this BMLT-2 target for the production of ^{89}Zr . A significant improvement in the ^{89}Zr -production yield compared to previous results [14]. We also developed a new method of elution of ^{89}Zr from hydroxamate resin that offers a biocompatible formulation of ^{89}Zr for preclinical and clinical studies. Finally, we also developed a short, simplified and one pot synthesis of the hydroxamate resin used for the separation of ^{89}Zr from the ^{89}Y target material.

2. Materials and Methods

2.1 Targetry details

A BMLT-2 target was employed for ^{89}Zr production as described previously [15]. The target consisted of a water-cooled, elongated Ta insert having target volume of 1.6 mL. The dual-foil design used helium cooling on a 0.2 mm aluminum degrader foil and a 0.025 mm Havar target window foil. The target was installed on a PETtrace cyclotron (GE HealthCare, Waukesha, WI) delivering 16.4 MeV protons. The incident proton energy to the target solution was approximately to 14 MeV. A semi-automated system was employed as described previously for target loading and unloading [14].

2.2 Chemicals

Yttrium nitrate ($\text{Y}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$) was purchased from Strem Chemicals (Newburyport, MA). Oxalic acid dehydrate [*TraceSELECT*®, $\geq 99.9999\%$ metals basis] was purchased from Sigma-Aldrich (St. Louis, MO). Nitric acid (70% purified by redistillation) $\geq 99.999\%$ trace metals basis as purchased from Fisher Scientific (Suwanee, GA). Chelex-100 resin (50-100 mesh, sodium form) was purchased from Bio-Rad. Accell Plus CM (300 Å, WAT 010740) weak cation exchange resin (carboxylate resin) was purchased from Waters Inc. (Milford, MA). The phosphate buffer used for ^{89}Zr elution was 1.2 M $\text{K}_2\text{HPO}_4/\text{KH}_2\text{PO}_4$ buffer (pH 3.5) prepared in-house using $\geq 99.999\%$ trace metals basis K_2HPO_4 and KH_2PO_4 , both purchased from Sigma-Aldrich (St. Louis, MO). Na_2HPO_4 and NaH_2PO_4 $\geq 99.999\%$ trace metals basis were also purchased from Sigma-Aldrich (St. Louis, MO).

2.3 Instrumentation

For determining radionuclidic purity, a high-purity germanium gamma spectrometer (Canberra, Meriden, CT) counter running Genie 2000 software was used. Sample radioactivity was measured using a CRC dose calibrator (489 setting, CRC-55tPET, Capintec, Ramsey, NJ). A Perkin Elmer ELAN DRC II ICP mass spectrometer (city, state) was employed to analyze trace metal contaminants. IR spectra were recorded as KBr pellets using a ThermoNicolet Avatar 370 FT-IR (Waltham, MA).

2.4 Method for ^{89}Zr separation and determination of specific activity

2.4.1 Synthesis of hydroxamate resin

The hydroxamate resin was synthesized by stirring the AccellTM Plus CM cation exchange carboxylate resin (2.00 g), methyl chloroformate (2.0 mL, 25.8 mmol) and triethylamine (2.0 mL, 14.3 mmol) in anhydrous dichloromethane (30 mL) at 0 °C for 30 min and then at room temperature for additional 90 min. The temperature of the mixture was further lowered to 0 °C before addition of hydroxylamine hydrochloride (0.6 g, 8.63 mmol) and triethylamine (2.0 mL, 14.3 mmol). The resultant mixture was stirred at room temperature for an additional 15 h. The solvent was removed under vacuum, and cold water was poured with constant stirring into the flask containing the functionalized resin. The resin was filtered, washed extensively with water, and dried under vacuum. Total amount of hydroxamate resin recovered was 1.9-2.0 g.

2.4.2 Validation of hydroxamate resin

Hydroxamate resin (75 mg) was packed into an empty cartridge having plastic frit on both the sides. The resin was activated with acetonitrile (8 mL), water (15 mL), and hydrochloric acid (2 mL 2 M) as described previously [13, 14] prior to testing the trapping efficiency. Different amounts of hydroxamate resin were evaluated for their efficiency in trapping of ^{89}Zr . The conversion of carboxylate group to a hydroxamate group on the resin was also characterized by infrared (IR) spectrometric analysis.

2.4.3 Separation of ^{89}Zr

Separation of ^{89}Zr from the irradiated $\text{Y}(\text{NO}_3)_3/\text{HNO}_3$ solution was achieved by trapping the ^{89}Zr on a custom-made hydroxamate column as described previously [14]. The $\text{Y}(\text{NO}_3)_3$ target material was removed

from the column by rinsing the resin with 2 M HCl (75 mL) and water (10 mL). Zirconium-89 was eluted from the resin using 1 M oxalic acid or a new elution reagent composed of 1.2 M $\text{K}_2\text{HPO}_4/\text{KH}_2\text{PO}_4$ (pH 3.5) (phosphate buffer). For the latter, ^{89}Zr elution was performed using a 2-step procedure whereby after rinsing with 2 M HCl followed by water to remove the Y target material, the ^{89}Zr -containing resin was first wetted with ~0.25 mL of phosphate buffer and allowed to interact on the column for 30-min before eluting the ^{89}Zr with an additional 1.75 mL of phosphate buffer. The eluted ^{89}Zr is in the form of ^{89}Zr -hydrogen phosphate ($^{89}\text{Zr}(\text{HPO}_4)_2$).

2.4.4 Specific activity

The specific activity (MBq/ μg) of ^{89}Zr was calculated based on measurement of total amount of Zr present in the final $^{89}\text{Zr}(\text{HPO}_4)_2$ solution using ICP-MS. The sample was assayed for other trace metals including Al, Ga, Fe, Cu, Ni, Zn, Co, Pb, Y, Sc, Rh, Mg, Lu, In, and Ca but only Fe, Y, Al and Zr were found to be present at detectable levels.

2.5 Statistical analysis

All values are given as mean $\pm$ standard deviation using Microsoft office excel program.

3. Results and Discussion

3.1 Optimized Production of ^{89}Zr

The enhanced heat dissipation capacity of the BMLT-2 target resulted in stabilized target pressure and avoidance of in-target precipitation issues during ^{89}Zr production for beam currents up to 40 μA . Taking a lead from our previous findings [14], we used 2 M yttrium nitrate in a 1.25 M nitric acid to minimize in-target precipitation. Initially, we tested different beam currents ranging from 10-40 μA by monitoring the change in-target pressure in a closed target system. Once we established that target pressure reached a steady state by 10-20 min of irradiation, we extended the irradiation time 2 h. The production rate per μA was increased by approximately 12% from 3.82 ± 0.37 MBq/ $\mu\text{A}\cdot\text{h}$ to 4.36 ± 0.60 MBq/ $\mu\text{A}\cdot\text{h}$, but due to the doubling of beam current the overall activity produced was found to be more than double in same 2 h of irradiation from 153.18 ± 15.1 MBq [14] to 348.88 ± 48.7 MBq (Table 1). The specific activity of the ^{89}Zr was not changed significantly from 464 ± 215 MBq/ μg [14] to 1186 ± 799 MBq/ μg (Table 2).

Analysis of metal contaminants in the ^{89}Zr product solution was carried out using ICP-MS (Table 3), and only small amounts of Al = 0.40-0.86 μg (n= 2), Fe = 1.22 $\pm$ 0.71 μg (n= 3), Y=0.29 μg (n= 1) All other metals were below detection limits.

Even though the production quantity of ^{89}Zr (~10 mCi in 2h) is doubled in a new solution target but it is still well below the calculated [16] and solid target production yields [13]. However, present production quantity (~10 mCi in 2h) was sufficient to meet the institutional need of ^{89}Zr for preclinical and small scale (up to 2-3 patients per day) clinical applications.

Table 1: ^{89}Zr production rates in first and second-generation solution targets in comparison to solid target.

	Molar concentration of $\text{Y}(\text{NO}_3)_3$ (M)	Beam Current (μA)	HNO_3 (M)	Decay Corrected EOB activity (MBq)	Production rate (MBq/ $\mu\text{A}\cdot\text{h}$)
TS-1650 target* (n=3)	2.75	20	1.50	153.1 $\pm$ 15.1 (4.14 $\pm$ 0.4 mCi)	3.82 $\pm$ 0.37
BMLT-2 target (n=7)	2.00	40	1.25	348.8 $\pm$ 48.7 9.4 $\pm$ 1.2mCi)	4.36 $\pm$ 0.60
Solid target**	-	15	-	1664.63 (44.99 mCi)	53.28
Calculated yield***	-	-	-	-	43

*data from Pandey et al. (14), **data from Holland et al. (13), *** data from SM Qaim (16)

All irradiations were performed for 2h. Yields were calculated before isotope separation at end of beam.

Table 2. Specific activities of purified ^{89}Zr in first and second-generation solution targets.

Specific Activity of ^{89}Zr produced using the TS-1650*** solution target (n=7) *(MBq/ μg)	Specific Activity of ^{89}Zr in a BMLT-2 target (n=3)** (MBq/ μg)
464 $\pm$ 215	1186 $\pm$ 799

* 2.75 M $\text{Y}(\text{NO}_3)_3$ in 1.5 N HNO_3 , 2 h irradiation at 20 μA beam current.

** 2.0 M $\text{Y}(\text{NO}_3)_3$ in 1.25 N HNO_3 , 2 h irradiation at 40 μA beam current.

*** A F-18 target designed by Bruce Technologies (Ref-14)

A purified sample of ^{89}Zr was analyzed on an HP-Ge gamma spectrometer for radionuclidic purity. The energy spectrum showed two photon peaks at 511 keV and 909 keV energies, both corresponding to ^{89}Zr . No other peaks were observed, indicating that the radionuclidic purity of ^{89}Zr was >99 % . However, when

purified samples were reanalyzed after 2-3 months from the date of productions, some trace quantities (<4 μCi) of longer lived-isotopes were found in < 0.031% only.

3.2 Resin synthesis and trapping efficiency

The previously described synthesis of the hydroxamate resin is a cumbersome process involving multiple reactions, purifications, and use of hazardous chemicals such as 2,3,5,6-tetrafluorophenol [13,17,18]. To address the need for a more practical and economical preparation of hydroxamate resin we developed a simplified, one-pot synthesis method using the same starting carboxylate resin. The carboxylate group on the resin was activated by methyl chloroformate and then converted into a hydroxamate functionality using hydroxylamine hydrochloride in presence of triethylamine [19]. The synthesis method was optimized for 2 g scale. We characterized the hydroxamate resin by both infrared spectroscopic analysis and ^{89}Zr trapping following the literature approach [13]. The asymmetric and symmetric stretching frequencies of the carbonyl of ($>\text{C}=\text{O}$) of the carboxylate moiety appeared at 1571.6 and 1403.7 cm^{-1} . The relative intensity of both the peaks was decreased compared to the non-functionalized resin while additional peaks at 1726 cm^{-1} and 1672 cm^{-1} , characteristic of the asymmetric and symmetric stretching frequencies of hydroxamate ($-\text{CONHOH}$) appeared in the hydroxamate functionalized resin compared to starting carboxylate resin [13]. Additionally, a medium to strong band at 1550 cm^{-1} for $-\text{N-H}$ deformation and C-N stretching vibration for amide II bands were reported for hydroxamic acids [20]. In our case, we also observed a strong band at 1552 cm^{-1} , confirming the presence of the hydroxamate group.

The resin was tested for ^{89}Zr trapping efficiency with different bed loads. A trapping efficiency of 93% was obtained with a 75 mg bed load. Higher amounts of resin (100-120 mg) increased the trapping efficiency to 96-97 %, but larger buffer volumes were then needed to elute the ^{89}Zr , which resulted in more dilute final solutions (see below). Thus 75 mg of resin was found to be optimal to obtain a highly concentrated solution of ^{89}Zr -hydrogen phosphate or ^{89}Zr -oxalate.

3.3 Isolation of ^{89}Zr as $^{89}\text{Zr}(\text{HPO}_4)_2$

Following the removal of Y from hydroxamate resin using 2 N HCl, ^{89}Zr is conventionally eluted from the resin in 1 M oxalic acid [13,17,18]. The toxicity of oxalic acid prevents this solution to be used directly in biological systems [13]. Holland et al. [13] described a method to convert ^{89}Zr -oxalate to $^{89}\text{ZrCl}_2$ using a QMA cartridge (anion exchange resin) followed by elution with 0.9% saline solution or 1 N HCl.

Hydrochloric acid gave good elution efficiency but required evaporation at 110 °C prior to the further use of the ^{89}Zr , whereas 0.9% saline solution gave only 22-38% elution efficiency [13]. There is, therefore, a need for an improved ^{89}Zr elution/formulation strategy for preparing ^{89}Zr in a biologically compatible medium. To address this issue we employed phosphate buffer to elute ^{89}Zr from the hydroxamate resin. The elution of ^{89}Zr was optimized using 1.2 M $\text{K}_2\text{HPO}_4/\text{KH}_2\text{PO}_4$ at pH 3.5, achieving $91.7 \pm 3.7\%$ elution efficiency using a total of 2 mL of buffer after an initial 30 min of equilibration on the column. Elution was performed in four 0.5 mL aliquots to provide an increased concentration of ^{89}Zr in one of the four fractions. For comparison to the conventional approach, a 1 M oxalic acid solution (1 mL) was also utilized to elute ^{89}Zr . The metal contaminants were analyzed in both the ^{89}Zr -hydrogen phosphate and ^{89}Zr -oxalate solutions, and found that both solutions contain similar small amounts of Al, Fe and Y (Table 3). Indeed, we have utilized this formulation strategy to effectively label stem cells without the need to reformulate ^{89}Zr eluted in oxalic acid [11].

Table 3: Metal impurities in the final ^{89}Zr product as a function of eluent.

Metal contaminants in ^{89}Zr -hydrogen phosphate eluent*	Metal contaminants in ^{89}Zr -oxalate eluent**
Al = 0.40-0.86 μg (n= 2), Fe =1.22 $\pm$ 0.71 μg (n= 3), Y=0.29 μg (n= 1)	Al = 2.39-5.38 μg (n= 2), Fe =1.10-1.20 μg (n= 2), Y=0.50 μg (n= 1)

*Total 4 samples were analyzed for a wide range of metal impurities (listed in method section) but detectable contaminants were present only in few samples and their numbers are written in the parenthesis.

** Total 2 samples were analyzed for a wide range of metal impurities (listed in method section) but detectable contaminants were present only in few samples and their numbers are written in the parenthesis.

Conclusions

In summary, the BMLT-2 target allowed doubling of the beam current for production of ^{89}Zr , resulting in a greater than 2-fold increase in production yield in comparison with a conventional liquid target. Specific activity of the isolated ^{89}Zr was not affected. Additionally, a simple one-pot synthesis of the hydroxamate resin and a new method of elution of ^{89}Zr from the hydroxamate resin with a phosphate buffer were developed to improve the practicality of ^{89}Zr production and provide a final formulation in a more biologically acceptable medium than the previously used oxalic acid solution.

Acknowledgments

This work was financially supported by a DOE grant to TRD/ABP DE-SC0008947 and the Department of Radiology, Mayo Clinic, Rochester, MN. MKP is grateful to the International Society of Radiopharmaceutical Sciences (ISRS) for awarding the outstanding poster award to this work at ISRS-Meeting Missouri 2015.

References

1. Ruyscher DD. Maastricht Radiation Oncology and VU University Medical Center. Non-invasive Imaging of Cetuximab-⁸⁹Zr uptake with PET: A Phase I Trial in Stage IV Cancer Patients. Clinicaltrials.gov, NCT00691548.
<https://clinicaltrials.gov/ct2/show/NCT00691548?term=NCT00691548&rank=1>
2. Oosting-Lenstra SF. University Medical Center Groningen and VHL Family Alliance. Visualizing Vascular Endothelial Growth factor (VEGF) Producing Lesions in Von Hippel-Lindau Disease (VHL image). Clinicaltrials.gov, NCT00970970.
<https://clinicaltrials.gov/ct2/show/NCT00970970?term=NCT00970970&rank=1>
3. Oosting-Lenstra SF. University Medical Center Groningen. VEGF imaging in Renal Cell Carcinoma (Renimage). Clinicaltrials.gov, NCT00831857.
<https://clinicaltrials.gov/ct2/show/NCT00831857?term=NCT00831857&rank=1>
4. Schroder CP. University Medical Center Groningen. VEGF Early Imaging for Breast Cancer. Clinicaltrials.gov, NCT00991978.
<https://clinicaltrials.gov/ct2/show/NCT00991978?term=NCT00991978&rank=1>
5. De Vries GE. University Medical Center Groningen. ⁸⁹Zr-bevacizumab PET imaging in Patients with Neuroendocrine tumors (NETPET). Clinicaltrials.gov, NCT01338090.
<https://clinicaltrials.gov/ct2/show/NCT01338090?term=NCT01338090&rank=1>
6. Chang AJ, Desilva R, Jain S, Lears K, Rogers B, Lapi S. ⁸⁹Zr-Radiolabeled Trastuzumab Imaging in Orthotopic and Metastatic Breast Tumors. *Pharmaceuticals (Basel)* 2012;5(1):79-93
7. Van de Watering FCJ, Rijpkema M, Perk L, Brinkmann U, Oyen WGJ, Boerman OC. Zirconium-89 Labeled Antibodies: A New Tool for Molecular Imaging in Cancer Patients. *BioMed Research International* 2014, article ID 203601, 13.
8. Sato N, S.L., Choyke P, Cell labeling using Zr-89 - comparison with In-111 oxine. *Proceedings World Molecular Imaging Congress, Savannah, GA, 2013*, 2013: p. P533.

9. Charoenphun P, Meszaros LK, Chuamsaamarkkee K, Sharif-Paghaleh E, Ballinger JR, Ferris TJ, Went MJ, Mullen GED, Blower PJ. [^{89}Zr]Oxinate for long-term in vivo cell tracking by positron emission tomography. *Eur J Nucl Med Mol Imaging*. 2015; 42: 278-87.
10. Davidson-Moncada J, Sato N, Hoyt Jr. RF, Reger RN, Thomas M, Clevenger R, Metzger ME, Donahue RE, Eclarinal PC, Szajek L, Griffiths GL, Dunbar CE, Choyke P, Childs R. A Novel method to study the vivo trafficking and homing of adoptively transferred NK cells in Rhesus Macaques and Humans. Proceedings of the 56th Annual Meeting of the American Society of Hematology, San Francisco, CA, December 6-9, 2014. Abstract #659.
11. Bansal A, Pandey MK, Demirhan YE, Nesbitt JJ, Crespo-Diaze RJ, Terzic A, Beffar A, DeGrado TR. *Eur J Nucl Med Mol Imaging Research* 2015;5:19.
12. Sadeghi M, Kakavand T, Taghilo M. Targetry of Y_2O_3 on a copper substrate for the non-carrier-added ^{89}Zr production via $^{89}\text{Y}(p,n)^{89}\text{Zr}$ reaction. *Kerntechnik*. 2010;75:298–302.
13. Holland JP, Sheh Y, Lewis JS. Standardized methods for the production of high specific-activity zirconium-89. *Nucl. Med. Biol.* 2009; 36:729–739.
14. Pandey MK, Engelbrecht HP, Byrne JP, Packard AB, DeGrado TR. Production of ^{89}Zr via the $^{89}\text{Y}(p,n)^{89}\text{Zr}$ reaction in aqueous solution: effect of solution composition on in-target chemistry. *Nucl. Med. Biol.* 2014;41:309-316.
15. Pandey MK, Byrne JF, Jiang H, Packard AB, DeGrado TR. Cyclotron production of ^{68}Ga via the $^{68}\text{Zn}(p,n)^{68}\text{Ga}$ reaction in aqueous solution. *Am J Nucl Med Mol Imaging* 2014;70: 2308-2312.
16. Qaim SM. Development of novel positron emitters for medical applications: nuclear and radiochemical aspects. *Radiochim. Acta* 2011; 99: 611-625.
17. Verel I, Visser GWM, Boellaard R, Stigter-van Walsum M, Snow GB, van Dongen GAMS. ^{89}Zr immuno-PET: comprehensive procedures for the production of ^{89}Zr -labeled monoclonal antibodies. *J Nucl Med* 2003;44:1271–1281.
18. Meijs WE, Herscheid JDM, Haisma HJ, Wijbrandts R, van Langevelde F, van Leuffen PJ, Mooy R, Pinedo HM. Production of highly pure no-carrier added ^{89}Zr for the labelling of antibodies with a positron emitter. *Appl Radiat Isotopes* 1994;45:1143–1147.

19. Pandey MK, DeGrado TR, Qian K, Jacobson MS, Clinton HE, Duclos Jr. RI, Gatley SJ. Synthesis and Preliminary Evaluation of N-(16-¹⁸F-fluorohexadecanoyl)ethanolamide (¹⁸F-FHEA) as a PET Probe of N-Acylethanolamine Metabolism in Mouse Brain. ACS Chem Neurosci, 2014; 5(9):793-802.
20. Socrates G. Infrared and Raman characteristic group frequencies: Tables and Charts. 3rd ed. Wiley, 2004.