An electrochemical generator for the continual supply of 213Bi from 225Ac for use in targeted alpha therapy applications

Fassbender, Michael Ernst
Akin, Andrew Christopher
Forrester, Ryan Anthony
Dutech, Guy Richard Henri
Mastren, Tara E

To be published in: Nuclear Medicine and Biology

DOI to publisher's version: 10.1016/j.nucmedbio.2024.108941

Journal Pre-proof

An electrochemical generator for the continual supply of 213Bi from 225Ac for use in targeted alpha therapy applications

Ryan Forrester, Guy Dutech, Andrew Akin, Michael E. Fassbender, Tara Mastren

PII: S0969-8051(24)00067-2

DOI: https://doi.org/10.1016/j.nucmedbio.2024.108941

Reference: NMB 108941

To appear in: *Nuclear Medicine and Biology*

Received date: 3 April 2024

Revised date: 25 June 2024

Accepted date: 8 July 2024

Please cite this article as: R. Forrester, G. Dutech, A. Akin, et al., An electrochemical generator for the continual supply of 213Bi from 225Ac for use in targeted alpha therapy applications, *Nuclear Medicine and Biology* (2023), https://doi.org/10.1016/j.nucmedbio.2024.108941

An Electrochemical Generator for the Continual Supply of ^{213}Bi from ^{225}Ac for use in Targeted Alpha Therapy Applications

Ryan Forrester[1], Guy Dutech[2], Andrew Akin[2], Michael E. Fassbender[2], and Tara Mastren[1*]

[1] Nuclear Engineering Program, University of Utah, 110 Central Campus Dr, Salt Lake City, UT 84112, USA

[2] Chemistry Division, Los Alamos National Laboratory, PO Box 1663, Los Alamos, NM 87545, USA

*Correspondence to:

Tara Mastren, 110 Central Campus Dr, Suite 2000B, Salt Lake City, UT 84112; Email: tara.mastren@utah.edu ; Phone: 801-581-7277

Abstract

Bismuth-213 is a radionuclide of interest for targeted alpha therapy and is supplied via a radiochemical generator system through the decay of ^{225}Ac. Radionuclide generators employ longer lived "parent" radionuclides to routinely supply shorter-lived "daughter" radionuclides. The traditional ^{225}Ac/^{213}Bi radiochemical generator relies on an organic cation exchange resin where ^{225}Ac binds to the resin and ^{213}Bi is routinely eluted. These resins degrade when they absorb large doses of ionizing radiation (>1 x 10^6 Gy/mg), which has been observed when the loading activity of ^{225}Ac exceeds 2.59*10^9 Bq (70 mCi). Herein we report the development of an electrochemical generator for the supply of ^{213}Bi that has the potential to overcome this limitation. Bismuth-213 spontaneously electrodeposits onto nickel foils in 0.1 M hydrochloric acid at 70ºC. Using this method, we were able to plate an average of 73 ± 4 % of the ^{213}Bi in solution and obtain a final ^{213}Bi recovery of 65 ± 8 % in 0.1 M citrate pH 4.5 via reverse electrolysis using titanium as the cathode. The recovered ^{213}Bi had an average radiochemical

purity of > 99.8 % and was successfully used to radiolabel DOTATATE with an average radiochemical yield of 85.1% (not optimized).

1. Introduction

Targeted alpha therapy (TAT) is a rapidly emerging field where alpha emitting radionuclides attached to targeting vectors are used to treat various diseases. Alpha particles are high in LET, which means that they deposit 4-5 MeV of energy within a short range (~10 cell lengths) resulting in a lethal dose to the targeted cancer cells.[1-3] The FDA approval of Xofigo© (^{223}Ra), an alpha emitting bone seeking agent that provides palliative treatment for bone metastases, has created a pathway for the use of alpha emitting radionuclides in the treatment of cancer and other diseases.[4]

Bismuth-213 ($t_{1/2}$ 46 minutes) is a radionuclide of interest for use in TAT applications and has been used in several clinical trials.[1, 5-7] One of the main hindrances to clinical trial applications utilizing ^{213}Bi is the current state of art used for its supply. Bismuth-213 is supplied with the use of a radionuclide generator system from its longer-lived parent ^{225}Ac ($t_{1/2}$ 10 days).[8] One of the major issues in the supply of ^{213}Bi is the production of radionuclide generators capable of providing large quantities of ^{213}Bi, > 3.7*10^{10} Bq (> 1 Ci), adequate to supply multiple patient doses. The traditional ^{225}Ac/^{213}Bi radiochemical generator relies on an organic cation exchange resin where ^{225}Ac binds to the resin and ^{213}Bi is routinely eluted with 0.1 M HCl/0.1 M NaI.[8-10] The high linear energy transfer (LET) associated with alpha decay damages the solid resin support causing breakthrough of ^{225}Ac resulting in generator failure at doses greater than 1 x 10^{6} Gy/mg.[11] Existing generators supply ~2.59*10^{9} Bq (70 mCi) of ^{213}Bi. However, with patient doses ranging from 3.7*10^{8} Bq to 3.7*10^{9} Bq (10-100 mCi), these

generators fail to supply sufficient ^{213}Bi to treat multiple patients and sometimes the dose must be delivered over time to allow ^{213}Bi to regenerate.[5, 6, 11, 12]

Several radionuclide generators have been developed for the separation of ^{213}Bi from ^{225}Ac. One of the more traditional approaches utilizes a column with actinide resin to bind the actinium and elute the ^{213}Bi which was subsequently captured on an MP-50 cation column to remove ^{221}Fr impurities. Bismuth-213 was then eluted in 0.1M HCl/0.1 M HI for subsequent use in radiolabeling studies[13]. Another popular approach is to employ an inorganic resin as the column material. Ondrak et al. developed a generator using a zirconium phosphate based resin that retained the ^{225}Ac while ^{213}Bi was routinely eluted with 10mM DTPA/5mM HNO_3 solution[14]. While nearly 100% recovery of ^{213}Bi was obtained with ~1 x 10^{-3}% ^{225}Ac, the use of DTPA could hinder future radiolabeling attempts as the binding affinity of Bi(III) to DTPA is quite large (log K_m 29.7).

Additionally, a couple reverse radionuclide generators (binding of ^{213}Bi by the column as opposed to having actinium fixed on the resin support) have been developed for the supply of ^{213}Bi with the potential to increase activity levels due to less radiolysis on the resin support. One from PNNL relies on an anion resin to bind the ^{213}Bi, allowing the actinium to flow through the column without interacting.[15] Another method employs the use of inorganic sorbents (zirconium and yttrium oxides) to absorb the ^{213}Bi ions out of solution.[16] A different group developed sulfonated carbon materials to achieve this goal.[17] While these inverse resins show promise, they are not without their limitations and these systems can be difficult to automate.[11]

To address these issues, we investigated a novel method to extract ^{213}Bi from the ^{225}Ac solution based on the premise that bismuth metal spontaneously plates onto nickel substrate.[18, 19] After spontaneous deposition of ^{213}Bi onto the nickel foil, it is then recovered by

electrochemical removal from Ni in a citrate solution. Electrochemical generators have been developed previously and shown promise for the $^{99}Mo/^{99m}Tc$, $^{90}Sr/^{90}Y$ and $^{188}W/^{188}Re$ radionuclide generator systems and are a promising area of development.[20-24] Using electrochemical systems for radionuclide generators allows the use of a metal framework for the separation of ^{213}Bi from ^{225}Ac. As metals are more resistant to radiation than resins traditionally used for separation, the potential exists for higher activity solutions to be utilized. Furthermore, binding ^{213}Bi from an equilibrium solution of $^{225}Ac/^{213}Bi$ reduces contact time with ^{225}Ac and its decay daughters, significantly reducing total dose to the substrate allowing for higher activity solutions.

2. Materials and Methods

2.1 Materials and Reagents

Nickel foil (99.9%) and titanium foil (99.5%) obtained from Goodfellow Cambridge Ltd. Stock solution of ^{225}Ac obtained from the National Isotope Development Center. Citric acid monohydrate (ACS reagent) was purchased from Fisher Scientific, ammonium acetate (99.99% trace metals basis) was purchased from Honeywell Fluka, and trisodium citrate dihydrate (molecular biology grade) was purchased from Sigma-Aldrich.

2.2 High Purity Germanium Spectrometry

Gamma-ray spectrometry was conducted using an EG&G Ortec Model GMX-35200-S HPGe detector system in combination with a Canberra Lynx Digital Signal Analyzer. Actinium was quantified using both the ^{221}Fr (218 keV) and ^{213}Bi (440 keV) gamma lines and ^{213}Bi was quantified using the 440 keV gamma line and decay corrected to time of separation. Actinium

quantification was measured once equilibrium was obtained with its daughters and decay corrected to time of separation. Detector response function determination and evaluation were performed using standards of radionuclide mixtures containing ^{241}Am, ^{109}Cd, ^{57}Co, ^{139}Ce, ^{203}Hg, ^{113}Sn, ^{137}Cs, ^{88}Y, ^{60}Co, traceable to the National Institute of Standards and Technology (NIST) and supplied by Eckert & Ziegler, Atlanta, GA, USA. Counting dead time was kept below 10%.

2.3 Evaluation of the Optimal Conditions for ^{213}Bi Spontaneous Deposition onto Nickel

Bismuth spontaneously deposits onto nickel foils in various media. For our purposes we examined which conditions lead to maximum deposition of bismuth onto nickel without co-deposition of ^{225}Ac and deposition of ^{213}Bi or ^{225}Ac onto the titanium cathode. We evaluated various media including 0.1 M HNO_3, 0.1 M HCl, and 0.1 M ammonium acetate pH 5. Briefly, the nickel and titanium foils were cleaned, polished, treated with 6 M HNO_3, and placed into a vial containing 1 mL of each solution. The foils were incubated for 20 minutes then removed from the solution, washed with 5 mL of fresh incubation solution and counted on an HPGe detector immediately after removal and 24 hours later to identify quantity of ^{213}Bi and ^{225}Ac bound. The 440.5 keV peak was used to identify ^{213}Bi and the 218.0 keV peak of ^{221}Fr ($t_{1/2}$ 4.8 minutes) used to identify ^{225}Ac. ^{213}Bi and ^{225}Ac counts were corrected for decay. These steps were repeated at various temperatures (70-90°C).

2.4 Evaluation of the Optimal Conditions for Recovery of ^{213}Bi from Nickel Foils

The removal of ^{213}Bi was facilitated by converting the nickel foil into an anode with a titanium foil being used as a cathode. Various voltages, times, and solutions were evaluated to maximize ^{213}Bi recovery. Initially, 1.5 mL of 0.1 M HCl, 0.1 M HNO_3, 0.1 M citrate pH 4.5, and 0.1 M

ammonium acetate pH 5 were explored for recovery of ^{213}Bi at 2.0 V. It was found that quantitative recovery of ^{213}Bi only occurred with the use of 0.1 M citrate pH 4.5. We then varied the voltage from 1-2.5 V to determine optimal voltage. We also measured the time dependance of applied voltage from 2-10 minutes. Finally, we assessed the dependance of the molarity of the citrate solution from 0.01 to 0.1 M on ^{213}Bi recovery.

2.5 Evaluation of an Electrochemical System as a Radionuclide Generator for the Separation of ^{213}Bi from ^{225}Ac

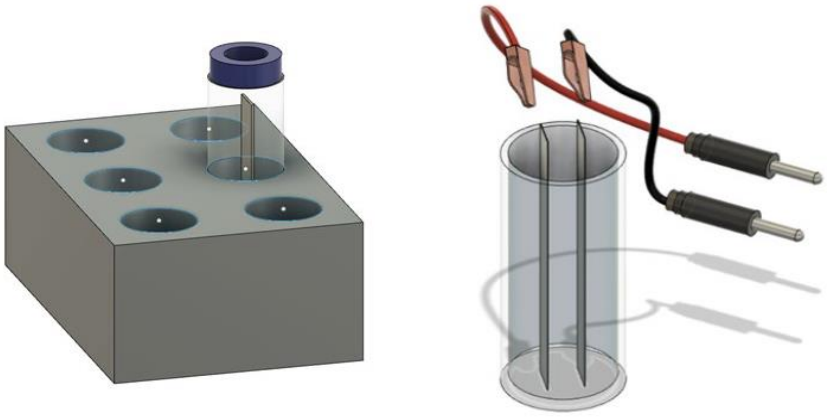

Figure 1: (left) A nickel foil in 0.1M HCl with ~555 kBq of ^{213}Bi in equilibrium with ^{225}Ac on a hot block at 70°C. (right) A nickel foil containing plated ^{213}Bi and a titanium foil in 0.1 M Citrate 4.5 pH being prepared for electrolysis with nickel on the positive (red) lead and titanium on the negative (black) lead.

Our electrochemical ^{225}Ac/^{213}Bi radionuclide generator system was set up as shown in Figure 1. Prior to use of the nickel (99.9% purity) and titanium foils (99.5 % purity) they were polished with a scrubbing pad and dipped in hot 6M nitric acid to remove any oxide layers. Then the

nickel was quickly rinsed, dried, and placed into 1.0 mL of 0.1 M HCl containing ~555 kBq (15 μCi) ^{213}Bi in equilibrium with ^{225}Ac. The nickel was incubated in the solution for 20 minutes at 70°C. Upon removal the nickel foil was rinsed once in 0.1 M HCl and counted on an HPGe detector to determine binding efficacy of ^{213}Bi. The incubation solution was also counted to determine the quantity of ^{213}Bi removed from the solution. The incubation solution was allowed to come to equilibrium and used in subsequent separations. The nickel foil was then connected to the anode and placed in 1.5 mL of a 0.1 M citrate solution pH 4.5 with a titanium foil that was connected to the cathode. A voltage of 2 V was applied for 6 minutes. The nickel was removed from the solution while voltage was still being applied to minimize redeposition of ^{213}Bi to the nickel foil. The nickel foil and electrolysis solution were counted via HPGe to determine recovery yields of ^{213}Bi. The solution was counted 24 hours later to determine "breakthrough" of ^{225}Ac. The system was run for a total of 35 times over the course of 30 days.

2.6 Complexation of Recovered ^{213}Bi to DOTATATE

Radiolabeling experiments with DOTATATE were performed using the recovered ^{213}Bi in the post electrolysis solutions. In each trial, 50 microliter aliquots (~18 kBq) of post-electrolysis solution were transferred to a small vial with 5 μL of DOTATATE (final concentration 6 μM/not optimized). The vial was added to a shaking incubator for 10 minutes at 70°. A 5 μL aliquot of the radiolabeled solution was spotted onto iTLC paper and developed in 0.1 M citrate solution. Once developed the iTLC paper was cut in half and each half was counted to determine binding of ^{213}Bi to DOTATATE. The [^{213}Bi]Bi-DOTATATE complex remained at the origin while any unbound bismuth travels to the top of the plate.

3. Results and Discussion

3.1 Evaluation of the Optimal Conditions for ^{213}Bi Spontaneous Deposition onto Nickel

Testing was done to identify the best solution for depositing ^{213}Bi to Ni foil without any ^{225}Ac co-deposition. 0.1 M HNO_3 and 0.1 M ammonium acetate were tested; however, under these conditions, significant levels of actinium (> 5%) bound to the surface of the nickel along with the bismuth, therefore pretreatment of the Ni foil in 6 M HNO_3 to remove the oxide layer was necessary. Even with pretreatment, small quantities of actinium (1-2%) still bound to the nickel foil with the use of these reagents. Experiments employing 0.1 M HCl as the solvent were more successful and ^{225}Ac did not significantly absorb (< 0.05 %) onto the surface of the Ni foil even in the absence of pretreatment. Further testing was done to establish the parameters under which optimal amounts of ^{213}Bi could be plated in a 0.1 M HCl solution. Experiments showed that when the Ni foil was left in 0.1 M HCl for 20 minutes, 80% of the ^{213}Bi adhered to the foil. When the Ni foil was left in for 55 minutes and 200 minutes, 80% of ^{213}Bi was found adhering to the foil. Therefore 20 minutes was determined to be sufficient for use in the radionuclide generator system. No stirring was applied to the system.

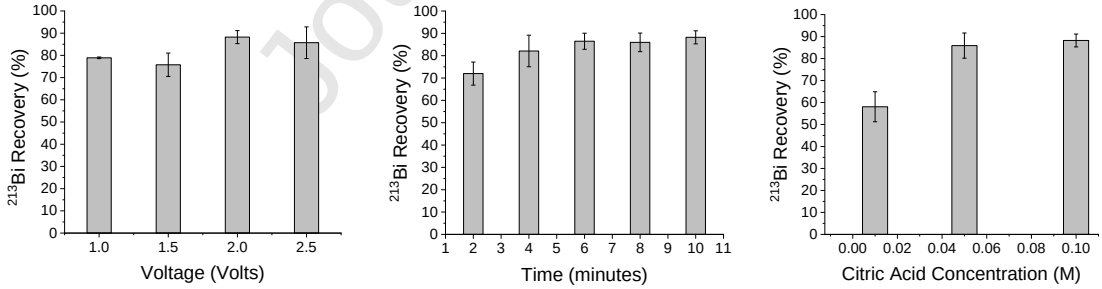

Figure 2: (left) ^{213}Bi recovery as a function of voltage, (middle) ^{213}Bi recovery at 2V as a function of time, and (right) ^{213}Bi recovery as a function of citrate concentration.

3.2 Evaluation of the Optimal Conditions for Recovery of ^{213}Bi from Nickel Foils

Removal of ^{213}Bi in 0.1 M citrate with no applied voltage resulted in a reduced recovery of 45%. Therefore, we decided to employ a titanium "cathode" to combine with the nickel "anode" to remove ^{213}Bi from the surface of the nickel foil. Titanium metal was chosen as the "cathode" due to its chemical inertness, low cost and to minimize reliance on critical materials. From these studies it was determined that 0.1 M citrate pH 4.5 resulted in the highest recovery of ^{213}Bi after reverse electrolysis. The recovery of ^{213}Bi into citrate solutions was explored as a function of voltage, time, and molarity of citrate. It was found that while varying the voltage from 1-2.5 volts, 2 and 2.5 volts resulted in the greatest removal of ^{213}Bi from the nickel foil resulting in ^{213}Bi recovery yields of 88% and 86% respectively (Figure 2). As the difference in recovery yields from 2 V and 2.5 V were not statistically significant, we moved forward with the lower voltage of 2 V. Next, the time dependance of applied voltage was evaluated from 2-10 minutes. Recovery yields increased from 2-6 minutes and then plateaued (Figure 2). Therefore, it was determined that 6 minutes was the optimal time for reverse electrolysis. Finally, we assessed the dependance on the molarity of the citrate solution from 0.01 to 0.1 M pH 4.5 of ^{213}Bi recovery. 0.01 M citrate resulted in low yields <60%, however both 0.05 and 0.1 M citrate solutions resulting in recovery yields of > 85% (Figure 2).

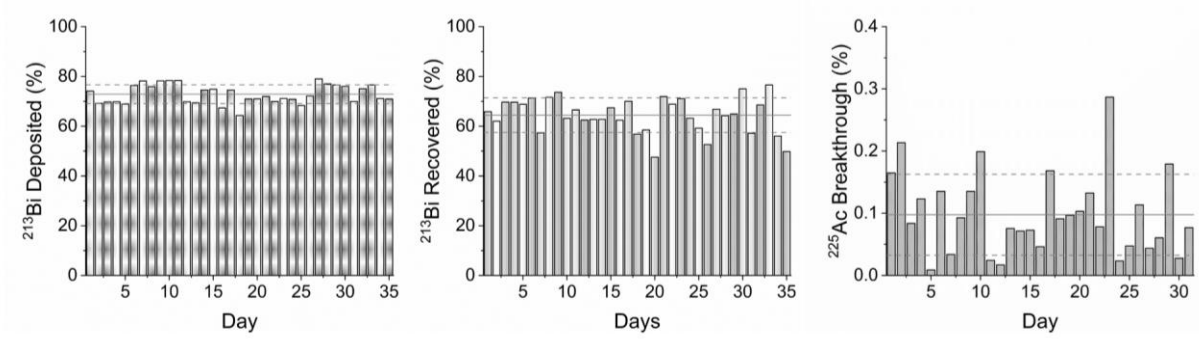

Figure 3: (left) ^{213}Bi deposition on nickel foil, (middle) overall ^{213}Bi recovery from the generator, and (right) ^{225}Ac breakthrough with daily "elutions" over a course of 35 days.

3.3 ^{225}Ac/^{213}Bi Electrochemical Generator Long-Term Analysis

Based on these results we decided the optimal conditions for the development of an ^{225}Ac/^{213}Bi radionuclide generator system would be as follows: 1) incubate foils in the ^{225}Ac/^{213}Bi solution at equilibrium in 0.1 M HCl at 70ºC for 20 minutes 2) rinse foils and transfer to a fresh 0.1 M citrate solution 3) connect the nickel foil to the anode and the titanium foil to the cathode. 4) apply constant voltage (2V) for 6 minutes 5) remove the foils prior to disconnecting voltage. The average plating yield of ^{213}Bi from the 0.1 M HCl solution was 73 ± 4 % (Figure 3). The average recovery of ^{213}Bi during reverse electrolysis from the nickel foil in the 0.1 citrate solution pH 4.5 was 89 ± 5 % resulting in a total ^{213}Bi recovery yield of 65 ± 8% (Figure 3). This is slightly lower than the 76 ± 3% yields currently obtained from the MP50 cation-based generators.[25] Breakthrough of ^{225}Ac in the final solution was found to be 0.10 ± 0.07 % (Figure 3) compared to 1 x 10^{-4} % in the "traditional" generator. Further optimization of our parameters, minimization of contact time, complete removal of oxide residues on the nickel and titanium foil and automation of our system could further minimize ^{225}Ac breakthrough. To demonstrate that ^{213}Bi recovered from our generator could be used in nuclear medicine applications and that the presence of citrate did not have a significant impact on radiolabeling, DOTATATE was radiolabeled with ^{213}Bi recovered from the generator. The average radiolabeling yields from three trials was 85 ± 8 % (Table 1) at an average molar activity of ~ 50kBq/nmol. The radiochemical yields are similar to previous results, however our molar activity is lower than what has been obtained with the "traditional" generator and was significantly lower in radioactivity (555 kBq vs 2.59 GBq). Future optimization of our radiolabeling experiments with higher quantities of ^{225}Ac will explore maximum obtainable specific activities.

Table 1: Radiolabeling yields for [^{213}Bi]Bi-DOTATATE corresponding to ~ 50 kBq/nmol.

Trial	[^{213}Bi]Bi-DOTATATE Radiolabeling Yields (%)
1	80.6
2	94.5
3	80.2
Average	85 ± 8

These results demonstrate the potential for an electrochemical based radionuclide generator system for ^{225}Ac/^{213}Bi. Using an electrochemical generator would potentially allow for larger activity levels of ^{225}Ac than the current state of art allows (70 mCi). Further optimization is needed to increase radiochemical yields of ^{213}Bi. This could be done with an automated microfluidic system with pumps that provide mixing in addition to increasing the surface area to solution ratio for the initial plating of ^{213}Bi. Nickel and titanium foils were evaluated for actinium deposition from the 0.1 M HCl solution, and it was found that both the foils absorbed actinium to some extent with more binding to the titanium than the nickel. This is likely due to the formation of an oxide layer as it has been shown that actinium has an affinity for titanium oxide.[26] Therefore it is believed that pursing avenues to completely eliminate the oxide layers on both the nickel and titanium foils or exploring other anode materials with less propensity for oxidation would help reduce ^{225}Ac breakthrough.

Additionally, metallic impurities can have a significant impact on radiolabeling yields. It is likely that nickel is added to the eluent as a result of reverse electrolysis. As the actinium used in this research had small quantities of ^{227}Ac, ICP-MS of our final solutions was not a possibility. However, as nickel has a significantly lower binding affinity to DOTA (log K_m 20.03) compared to bismuth (log K_m 30.4), we do not expect it to compete significantly with binding. This has been shown with other metallic impurities where the binding affinity is > 10 orders of magnitude lower.[27, 28] However, the same authors suggest that the magnitude of the stability constant

does not always correspond to the capacity of a metal to displace a radiolabeled complex thus future work should include the influence of nickel to radiolabeling yields for [^{213}Bi]Bi-DOTATATE.

Metals are known to be more radioresistant than organic based resins such as MP-50. In addition to being resistant to radiolysis, plating the ^{213}Bi out of solution results in significantly lower contact times and reduced radiation exposure. The combination of these effects results in a radionuclide generator system that has the potential to overcome the 2.59*10^{9} Bq (70 mCi) activity limits currently available. Future work will focus on the development of a microfluidic system, which would minimize the volume of the ^{225}Ac/^{213}Bi solution, while maximizing contact surface area of the nickel foil. Additionally, slight agitation of the solution when in contact with the nickel foil could help to increase bismuth plating yields.

Conclusions

In conclusion, herein we have reported an electrochemical based radionuclide generator system for the repeated supply of ^{213}Bi. This system resulted in an average ^{213}Bi radiochemical yield of 65 ± 8 % and an average ^{225}Ac breakthrough of 0.10 ± 0.07 %. Furthermore, the ^{213}Bi obtained from the generator was used to radiolabel DOTATATE with an average radiochemical yield of 85 ± 8 % and a molar activity of 50 kBq/nmol.

Acknowledgements

This work funded by the Los Alamos National Laboratory's Directed Research and Development

Program, Exploratory Research, (LDRD 20-165ER). Actinium-225 used in this research was supplied by the U.S. Department of Energy Isotope Program, managed by the Office of Isotope R&D and Production.

References

[1] Birnbaum ER, Fassbender ME, Ferrier MG, John KD, and Mastren T. Actinides in medicine. Encyclopedia of inorganic and bioinorganic chemistry 2011:1-21.

[2] Elgqvist J, Frost S, Pouget J-P, and Albertsson PJFio. The potential and hurdles of targeted alpha therapy–clinical trials and beyond. Frontiers in Oncology 2014;3:324.

[3] Kim Y-S and Brechbiel MWJTb. An overview of targeted alpha therapy. Tumour Biol 2012;33:573-90.

[4] Kluetz PG, Pierce W, Maher VE, Zhang H, Tang S, Song P, et al. Radium Ra 223 dichloride injection: US Food and Drug Administration drug approval summary. Clin Cancer Res 2014;20:9-14.

[5] Morgenstern A, Bruchertseifer F, and Apostolidis C. Targeted alpha therapy with 213Bi. Current Radiopharmaceuticals 2011;4:295-305.

[6] Jurcic JG. Clinical studies with bismuth-213 and actinium-225 for hematologic malignancies. Current radiopharmaceuticals 2018;11:192-9.

[7] McDevitt MR, Finn RD, Ma D, Larson SM, and Scheinberg DA. Preparation of α-emitting 213Bi-labeled antibody constructs for clinical use. J Nucl Med 1999;40:1722-7.

[8] McDevitt MR, Finn RD, Sgouros G, Ma D, and Scheinberg DA. An 225Ac/213Bi generator system for therapeutic clinical applications: construction and operation. Appl Radiat Isotopes 1999;50:895-904.

[9] Ma D, McDevitt MR, Finn RD, and Scheinberg DA. Breakthrough of 225Ac and its

radionuclide daughters from an 225Ac/213Bi generator: development of new methods, quantitative characterization, and implications for clinical use. Appl Radiat Isotopes 2001;55:667-78.

[10] Morgenstern A, Bruchertseifer F, and Apostolidis C. Bismuth-213 and actinium-225–generator performance and evolving therapeutic applications of two generator-derived alpha-emitting radioisotopes. Current radiopharmaceuticals 2012;5:221-7.

[11] Vasiliev A, Ermolaev S, Lapshina E, Betenekov N, Denisov E, and Zhuikov B. Various Chromatographic Schemes for Separation of 213Bi from 225Ac☆☆☆. Journal of Medical Imaging and Radiation Sciences 2019;50:S90.

[12] Kratochwil C, Giesel F, Bruchertseifer F, Mier W, Apostolidis C, Boll R, et al. 213 Bi-DOTATOC receptor-targeted alpha-radionuclide therapy induces remission in neuroendocrine tumours refractory to beta radiation: a first-in-human experience. Eur J Nucl Med Mol I 2014;41:2106-19.

[13] Ermolaev S, Skasyrskaya A, and Vasiliev A. A Radionuclide Generator of High-purity Bi-213 for Instant Labeling. Pharmaceutics 2021;13:914.

[14] Ondrák L, Fialová KO, Sakmár M, Vlk M, Bruchertseifer F, Morgenstern A, et al. Development of 225Ac/213Bi generator based on α-ZrP-PAN composite for targeted alpha therapy. Nuclear Medicine and Biology 2024;132:108909.

[15] Bray LA, Tingey JM, DesChane JR, Egorov OB, Tenforde TS, Wilbur DS, et al. Development of a unique bismuth (Bi-213) automated generator for use in cancer therapy. Ind Eng Chem Res 2000;39:3189-94.

[16] Vasiliev AN, Ermolaev SV, Lapshina EV, Zhuikov BL, and Betenekov ND. 225Ac/213Bi generator based on inorganic sorbents. Radiochim Acta 2019;107:1203-11.

[17] Zhu H, Heinitz S, Eyley S, Thielemans W, Binnemans K, Mullens S, et al. Selective separation of Bi3+ from La3+/Ac3+ by sorption on sulfonated carbon materials for use in an inverse 225Ac/213Bi radionuclide generator: Batch and column tests. Chemical Engineering Journal 2023;468:143416.

[18] Hummrich H, Banik NL, Breckheimer M, Brüchle W, Buda R, Feist F, et al. Electrodeposition methods in superheavy element chemistry. rca-Radiochimica Acta 2008;96:73-83.

[19] Zhong Q, Puigcorbé V, Sanders C, and Du J. Analysis of 210Po, 210Bi, and 210Pb in atmospheric and oceanic samples by simultaneously auto-plating 210Po and 210Bi onto a nickel disc. Journal of environmental radioactivity 2020;220:106301.

[20] Dash A and Chakravarty R. Electrochemical separation: promises, opportunities, and challenges to develop next-generation radionuclide generators to meet clinical demands. Ind Eng Chem Res 2014;53:3766-77.

[21] Chakravarty R, Dash A, Kothari K, Pillai MA, and Venkatesh M. A novel 188W/188Re electrochemical generator with potential for medical applications. rca-Radiochimica Acta 2009;97:309-17.

[22] Chakravarty R, Pandey U, Manolkar RB, Dash A, Venkatesh M, and Pillai MA. Development of an electrochemical 90Sr–90Y generator for separation of 90Y suitable for targeted therapy. Nucl Med Biol 2008;35:245-53.

[23] Chakravarty R, Dash A, and Venkatesh M. A novel electrochemical technique for the production of clinical grade 99mTc using (n, γ) 99Mo. Nucl Med Biol 2010;37:21-8.

[24] Azadbakht B, Afarideh H, Ghannadi-Maragheh M, Asgari M, and Bahrami-Samani A. Development of an electrochemical 188W/188Re generator as a technique for separation and

purification of 188Re in radiopharmaceutical applications. Appl Radiat Isotopes 2016;118:331-7.

[25] Centre JR, Elements IfT, Fanghänel T, Babelot J, and Magill J. Institute for transuranium elements – Annual report 2006: Publications Office of the European Union,2007.

[26] Brown MA. Metal oxide sorbents for the separation of radium and actinium. Industrial & Engineering Chemistry Research 2020;59:20472-7.

[27] Walczak R, Gawęda W, Dudek J, Choiński J, and Bilewicz A. Influence of metal ions on the 44 Sc-labeling of DOTATATE. Journal of Radioanalytical and Nuclear Chemistry 2019;322:249-54.

[28] Asti M, Tegoni M, Farioli D, Iori M, Guidotti C, Cutler CS, et al. Influence of cations on the complexation yield of DOTATATE with yttrium and lutetium: a perspective study for enhancing the 90Y and 177Lu labeling conditions. Nuclear medicine and biology 2012;39:509-17.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Tara Mastren reports financial support was provided by Los Alamos National Laboratory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Graphical abstract