Proton induced production and radiochemical isolation of ^{44}Ti from scandium metal targets for $^{44}\text{Ti}/^{44}\text{Sc}$ generator development

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ABSTRACT

Scandium-44g (half-life 3.97 h) shows promise for application in Positron Emission Tomography (PET), due to favorable decay parameters. One of the sources of ^{44g}Sc is the $^{44}\text{Ti}/^{44g}\text{Sc}$ generator, which can conveniently provide this radioisotope on a daily basis at a diagnostic facility. Titanium-44 (half-life 60.0 a), in turn, can be obtained via proton irradiation of scandium metal targets. A substantial ^{44}Ti product batch, however, requires high beam currents, long irradiation times and an elaborate chemical procedure for ^{44}Ti isolation and purification. This study describes the production of a combined 175 MBq (4.7 mCi) batch yield of ^{44}Ti in week long proton irradiations at the Los Alamos Isotope Production Facility (LANL-IPF) and the Brookhaven Linac Isotope Producer (BNL-BLIP). A two-step ion exchange chromatography based chemical separation method is introduced: first, a coarse separation of ^{44}Ti via anion exchange sorption in concentrated HCl results in a $^{44}\text{Tc}/\text{Sc}$ separation factor of 10^2 - 10^3 . A second, cation exchange based step in HCl media is then applied for ^{44}Ti fine purification from residual Sc mass. In summary, this method yields a 90-97% ^{44}Ti recovery with an overall Ti/Sc separation factor of $\geq 10^6$.

1. Introduction

Scandium-44g is a promising radionuclide with favorable characteristics for PET imaging applications (E_{β^+} -mean 0.632 MeV, positron branching 94.27%) [1]. The half-life of 3.97 h matches the rate of some slower biological processes involving peptides and antibody fragments, which renders ^{44g}Sc suitable for the radiolabeling of small to medium biomolecules [2-5]. Scandium does possess other radioisotopes suitable for imaging and therapy, namely nuclear isomer ^{44m}Sc (half-life 58.6 h [6]), ^{43}Sc (3.891 h, [7]) and ^{47}Sc (3.349 d, [8, 9]), supporting the

potential for a scandium isotope theranostic system [10-12]. In recent studies, imaging utilizing ^{44g}Sc labeled radiopharmaceuticals was evaluated pre-clinical and clinical studies. Results indicated similarity, even slight superiority over the analogous ^{68}Ga based system [13, 14] in terms of image quality and time for logistic and compound preparation. The chelator 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic (DOTA) is frequently applied to attach scandium radioisotopes to biomolecules [15,16]; however, several other chelators have also been tested [17,18]. *In vitro* and *in vivo* studies with DOTA have shown that stability of ^{44g}Sc labeled compounds is adequate to conduct imaging [15-17]. Production methods for ^{44g}Sc using low energy protons include both direct and indirect routes (Table 1). Reaction cross sections for the $^{44}\text{Ca}(p,n)^{44m,g}\text{Sc}$ and $^{45}\text{Sc}(p,2n)^{44}\text{Ti}$ pathways have been reported in the literature [19-23].

[Table 1]

The direct production via proton or deuteron irradiation of natural or enriched calcium with low energy protons has been investigated by several groups [24-28]. As compared to $^{44}\text{Ca}(d,2n)^{44m,g}\text{Sc}$, the proton induced process $^{44}\text{Ca}(p,n)^{44m,g}\text{Sc}$ does have the advantage of higher physical yield and lower $^{44m,g}\text{Sc}/^{44g}\text{Sc}$ isomeric ratio [23]. This production route results in a relatively high production yield; however, it requires daily irradiations to support a constant supply of short-lived ^{44g}Sc . Moreover, several other scandium isotopes are co-produced during the irradiation of calcium. One by-product is nuclear isomer ^{44m}Sc ($t_{1/2}$ 58.6 h), which can be used as *in vivo* generator for the ground state since it undergoes isomeric transition [29]. After production, ^{44g}Sc needs to be isolated from the Sc target material. Several methods based on ion exchange and solid phase extraction chromatography have been reported [24-28]. Reported

separations resulted in sufficient yields with a high degree of radionuclidic purity, a requisite condition for the ^{44g}Sc labeling of biomolecules.

Scandium-44g can also be obtained via the decay of ^{44}Ti ($t_{1/2} = 60.0$ a) [30]. While this generator system provides a source of ^{44g}Sc without the need for daily irradiations (providing an attractive alternative for PET facilities that lack in-house irradiation capabilities), it also requires a rather high loading activity of long-lived parent ^{44}Ti . Titanium-44 can be obtained from proton or deuteron irradiation of Sc targets, and the recovery of ^{44}Ti from the bulk target material mandates an efficient Ti/Sc chemical separation process. A further prerequisite for a $^{44}\text{Ti}/^{44}\text{Sc}$ generator is the development of a robust Ti/Sc solid-liquid separation system allowing maximal elution of ^{44}Sc with minimal breakthrough of parent ^{44}Ti . Several research groups have reported on the production of ^{44}Ti by the proton irradiation of natural scandium [31, 32]. Radiochemical methodologies for the purification of titanium from a bulk scandium target have been proposed, including methods of ion exchange [31, 32] and chelation resin sorption [33]. A Ti/Sc separation concept on the basis of “ZR resin” sorption has recently been reported [34].

The Los Alamos Isotope Production Facility (LANL-IPF) and the Brookhaven Linac Isotope Producer (BNL-BLIP) routinely irradiates targets stacks for isotope production. The low proton energy slots (<40 MeV) located downstream (at the back) of the stacks were used for the production of generator parent ^{44}Ti at both LANL and BNL from scandium metal targets. Irradiated targets were used to develop a process for the separation of ^{44}Ti from bulk scandium. In this paper, we report the results of these scandium target irradiations and the subsequent chemical processing for ^{44}Ti recovery and purification. In addition to the published “ZR resin”

based separation method, we herein introduce an alternative ion exchange methodology which comprises a combination of anion and cation chromatography: anion exchange chromatography in HCl media was used for the bulk scandium mass removal while cation exchange chromatography was used for ^{44}Ti fine purification. Depending on the desired final form of ^{44}Ti , either method (ZR resin or ion exchange based) may be used.

2. Materials and methods

2.1 Target design

Scandium metal disk sputtering targets for irradiation were manufactured to size by Symcon Inc (Charlotte, NC, USA). The BNL target had a mass of 17.5 ± 0.2 g and a purity of >99.99% with an ICP-OES trace analysis profile of [ppm; per manufacturer's certificate of analysis]: Ti (2); Fe (35); Ni (10); Nb (0.1); Ta (0.2). The LANL target had a mass of 27.04 ± 0.25 g and a purity of 99.99%. The ICP-OES trace analysis profile was [ppm; per manufacturer's certificate of analysis]: Ti (13); Fe (190); Ni (50); Nb (10); Ta (1000). Scandium metal targets were individually designed to accommodate for beam diameter differences and other geometry constraints at IPF and BLIP.

For the irradiation at LANL-IPF the Sc metal disk, thickness 4.47 mm, was encapsulated in Inconel canisters by Moddrell Manufacturing Management, LLC, Pasco, WA. Inconel canisters consisted of two 0.020 inch (0.508 mm) thick windows, electron beam welded under vacuum to a 0.100 inch (2.54 mm) thick Inconel ring. For irradiation at BLIP, the Sc disk, 0.060 inch (1.52 mm) thickness, was encapsulated in aluminum. The capsule comprised two 0.020 inch (0.508 mm) thick windows electron beam welded under vacuum to the 0.100 inch (2.54 mm) aluminum

ring. The LANL targets were designed to stop the beam and capture the whole cross section curve below 30 MeV while BNL target was designed to capture only a portion of $^{45}\text{Sc}(p,2n)$ excitation function. Target thermal analyses were conducted as described earlier [35].

2.2 Gamma-ray spectrometry

Gamma-ray spectrometry at LANL and BNL was carried out using HPGe detectors manufactured by ORTEC (Oak Ridge, TN USA). At LANL the measurement was conducted using an EG&G Ortec Model GMX-35200-S HPGe detector system in combination with a Canberra Model 35-Plus multichannel analyzer. 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%. At BNL, the measurements were carried out using an Ortec GEM13180-P10 model with relative efficiency of about 10% at 1333 keV. Similarly, the response function determination was carried out with NIST traceable mixed gamma standard.

Titanium-44 content in the target solution was determined using the 1157.02 keV $^{44\text{g}}\text{Sc}$ γ -line [cf. Ref. 1] after the target activity was allowed to abate for a period of >40 days for the decay of the directly produced $^{44\text{m,g}}\text{Sc}$. In general, throughout the separation study, ^{44}Ti was quantitatively determined via $^{44\text{g}}\text{Sc}$ detection. The in-growth of $^{44\text{g}}\text{Sc}$ was ensured by allowing adequate time before measurement. For qualitative ^{44}Ti direct measurements, the low energy 67.868 and 78.323 keV γ -lines were used. Scandium distribution was followed using co-produced tracer ^{46}Sc

(889.277 keV and 1120.545 keV γ -lines) tracer, which was co-produced via $^{45}\text{Sc}(n,\gamma)$ in the target from the interaction with secondary neutrons generated during irradiations. Radionuclidic impurity ^{56}Co , which stemmed from Fe and Ni traces in the Sc target, was tracked by the 846.77 keV γ -line.

2.3 Chemical reagents

All chemicals were used without further purification. Nitric acid Optima grade was purchased from Fisher Scientific (Pittsburgh, PA, USA). Hydrochloric acid (HCl) of 11.3 M concentration was purchased from Sigma Aldrich (St. Louis, USA); 12.3 M HCl (Ricca Chemical) was obtained from Fisher Scientific. Deionized water ($\geq 18\text{ M}\Omega\text{ cm}$) was prepared on-site with an installed Millipore water purification system (LANL) and a Milli-Q Advantage A10 Water Purification System (BNL). Cation exchanger resin AG 50WX8, 200-400 mesh and anion exchanger resin AG1X8, 100-200 and 200-400 mesh were obtained from Biorad (Hercules, CA, USA). Resins were loaded into Biorad Econo-Pac® Chromatography Columns (14 cm height, 1.5 diameter x 12 cm loading height) and equilibrated with the respective matrices prior to all ion exchange procedures.

2.4. Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES)

Determination of stable contaminants was carried out via Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES) using a Shimadzu ICPE-9000 instrument equipped with a 2 cm x 2 cm CCD detector calibrated on the day of use. Instrument responses were calibrated to known scandium concentrations in calibration solutions; calibration solutions were prepared from certified stocks, purchased from Fisher Scientific (Pittsburgh, PA, USA). Analyses were

performed in triplicate and based on a 30 s sample exposure time. Output data were managed and analyzed using the ICPE Solutions software version 1.01 (Shimadzu Corp. 2005).

3. Experimental

3.1 Irradiations

At both facilities, the targets were irradiated in the low energy slot behind routine production targets using a circular rastered beam at IPF and a focused Gaussian shaped beam at BLIP. The energy degradation in the target stack was calculated using dE/dx values generated by SRIM 2008 software (Table 2).

[Table 2]

3.2 Radiochemical separations

Only a portion of the irradiated Sc material (~20% of the total mass) was used for the radiochemical studies in this work. The remainder of the material was utilized for alternative Ti/Sc chemical separation and $^{44}\text{Ti}/^{44}\text{Sc}$ generator development [30]. Chemistry development experiments were carried out at LANL, while a scaled-up experiment was conducted at BNL. For chemical separation development, a Sc target dissolution solution aliquot of 1.0 g was used at LANL, while a 3.6 g dissolution aliquot was used at BNL for the scaled-up separation experiment.

3.2.1 Target dissolution

High dose rates mandated that the irradiated targets were opened and dissolved within a hot cell and handled remotely. The target was cut open using a rotary cutting tool in a hot cell,

and the scandium disc was removed from the Inconel capsule. The target was then placed in a 500 mL polyester bottle, and portions of 6 M HCl (10-15 mL; total volume 380 ± 10 mL) were added until full dissolution was achieved and the solution appeared clear. The target dissolution solution was passed through a cellulose nitrate filter (0.45 μm) and the filter was washed with additional 6 M HCl (25 mL) to recover any traces of ^{44}Ti . Washes were combined with the target solution, and an aliquot (235 μl) of the solution was analyzed via γ -ray spectrometry to determine the overall physical yield.

The BNL irradiated Sc target was cut open, and the dissolution was started by the addition of 2M HCl (40 mL). Further HCl was added (9-10 M; 10-20 mL portions) when the dissolution rate appeared to have slowed down until the dissolution was complete. The resultant solution was filtered through a Whatman® quantitative filter paper. The solid residue was washed with 2M HCl, and the washes were combined with the target solution. An exact aliquot of the resultant solution was removed and assayed on a HPGe detector. The total volume of the solution was determined from its mass and density; the density was determined by measuring the weight of an exact target dissolution solution aliquot ($5.0 \pm .35$ mL).

3.2.2 Separation of ^{44}Ti from the target dissolution solution

Separation from 1.0g of Sc. An aliquot of the target solution containing 1.0 ± 0.2 g of Sc in 6 M HCl (15 mL) was evaporated to dryness and then re-dissolved in 11.3 M HCl (100 mL). The solution was then loaded on an AG1X8 anion exchange column (15 mL bed volume, preconditioned with 11.3 M HCl, 200-400 mesh, Cl^- form). The column effluent was collected (f1) and subjected to γ -ray spectrometry to confirm the absence of detectable ^{44}Ti . The column was then washed with 50 mL of 11.3 M HCl (f2) to further remove Sc. The ^{44}Ti loaded column

was then removed from the hot cell and ^{44}Ti was eluted with 70 mL of 4 M HCl (f3-f8) in a radiological fume hood.

Separation from 3.6 g of Sc. Based on the 1.0 g experiment, a glass column containing anion exchange resin AG1X8 (200-400 mesh, Cl⁻, 40 mL) was equilibrated in 12.3 M HCl. An aliquot of the target solution (corresponding to 3.6 g of Sc content) was evaporated to dryness and re-dissolved in 80 mL of 12.3 M HCl. The solution was loaded on the column and the effluent collected. The column was washed with 2.75 bed volumes of 12.3 M HCl, which was collected in 90 mL and 20 mL portions. Titanium-44 was further eluted with 2.5 bed volumes of 8 M HCl.

3.2.3 Fine purification of ^{44}Ti from Sc mass

Titanium-44 from the 1.0g Sc experiment. Purification of ^{44}Ti from traces of scandium was carried out on a cation exchange column in 4M HCl. Fractions f3-f8 from 3.2.2 were sequentially loaded onto a cation exchanger column AG50WX8 (10 mL resin bed, 200-400 mesh, H⁺ form) and collected in 10 to 15 mL fractions (f9-f14) to track the distribution of Ti(IV) and Sc(III). The column was then washed with an additional 4 M HCl (f15-f17) amounting to a total of 30 mL. If breakthrough of ^{46}Sc was detected, purification of the corresponding fractions was repeated on a smaller cation exchange column (AG50X8, 200-400 mesh, H⁺ form, 5 mL) without preconditioning.

Titanium-44 from the 3.6g Sc experiment. A similar fine purification experiment was carried out in 1M HCl, where ^{44}Ti was separated from ~300 mg of residual Sc on a cation exchange column. The solution was evaporated, then brought up in 10 mL of 1M HCl and loaded onto a 17 mL bed volume column cation exchanger (AG50X8, 200-400 mesh) prepared in 0.5 M HCl. The column was washed with 1M HCl, and fractions were collected in 10 mL increments.

225

226   3.2.4   *Titanium-44 separation from ^{56}Co*

227   **Separation from 1.0g of Sc.** Anion exchange was utilized for the separation of (tetravalent)
228   ^{44}Ti from (divalent) ^{56}Co . Cobalt-56 was a by-product that originated from the relatively high Fe
229   and Ni content in the LANL Sc target as well as possible contribution from recoil from Inconel
230   capsule activation. Fractions from the previous experiments containing ^{44}Ti were evaporated to
231   dryness and re-dissolved in 28 mL of 8 M HCl. This solution was loaded on a pre-conditioned
232   anion exchange column (AG1X8, 100-200 mesh, Cl^- form, 10 mL). Four fractions (~7 mL each,
233   f1-f4) were collected, and the column was eluted with 8 M HCl (9 mL each, 35 mL total). As
234   the BNL (Al encapsulated) target was concerned (material from the 3.6 g experiment), no ^{56}Co
235   contamination was detected.

236

237   **4.   Results**

238   4.1   *Target irradiation and radionuclide yields*

239   Upon completion of the proton irradiations, the targets were visually inspected for integrity
240   and heat marks. Both targets exhibited heat marks corresponding to the beam pattern in each
241   facility (please refer to the Supplementary data for photographs). The LANL target had a heat
242   mark in the shape of a ring created by the rastered IPF beam, while the BNL target showed a heat
243   mark in the center of the target consistent with the Gaussian shaped focused beam at BLIP. The
244   primary long term dose rate contributor in both cases was ^{46}Sc produced via the $^{45}\text{Sc}(n, \gamma)^{46}\text{Sc}$
245   secondary neutron activation. The only other radionuclidic impurity observed in the LANL-IPF
246   target was ^{56}Co , formed via $\text{Fe}(p, x)$ and $\text{Ni}(p, x)$ from Fe and Ni traces in the Sc target material
247   (see Section 2.1). The γ -ray spectrum of the LANL target dissolution solution along with target

photographs prior to proton irradiation and the cut open target are available as supplemental material. Table 3 presents the measured activities and the ratio [in %] of the experimental thick target yield for ^{44}Ti as calculated from $^{45}\text{Sc}(p,2n)^{44}\text{Ti}$ reaction cross sections [22] assuming the production energy windows given in Table 1.

[Table 3]

4.2 Target dissolution

A vigorous reaction was observed upon addition of the first 10-15 mL portions of 6 M HCl to the Sc target. The reaction was accompanied by hydrogen gas evolution and was sustainable at room temperature.

4.3. Separation of ^{44}Ti from the Sc target dissolution solution

Separation from 1g of Sc. Fig. 1 depicts the anion exchange column elution profile. The initial loading effluent (f1) and the 11.3 M HCl wash (f2) combined contained all scandium, with f1 containing 82% and f2 18% of the ^{46}Sc activity. While ^{44}Ti was not detectable in fraction f1, about 3% of the initial ^{44}Ti activity was detected in fraction f2. The successive elution fractions f3-f7 contained $\geq 97\%$ of the ^{44}Ti activity. The Ti/Sc separation factor determined for this column was 10^2 . Scandium elution commenced after $\sim 82\text{mL}$ of the target solution was passed through the anion exchange column. It should be noted that ^{56}Co eluted with the ^{44}Ti .

[Figure 1]

Separation from 3.6 g of Sc. No ^{44}Ti breakthrough was observed in the 3.6 g Sc mass scale up experiment which was carried out with more concentrated (12.3 M) HCl media using a larger

bed volume (40 mL) of anion exchange resin. More than 95% of the scandium was found in the combined loading effluent and wash (Table 4). About 90% of the ^{44}Ti was found in the 4MHCl elution fractions along with some residual Sc.

[Table 4]

4.4 Titanium-44 fine purification

The cation exchange column feed from the 1.0g Sc experiment (Chapter 3.2.3) contained about 10 mg of stable Sc. The initial column effluent eluted most of the ^{44}Ti ($\geq 95\%$) (f9-f14); the last effluent fraction (f14) contained detectable ^{46}Sc activity ($\leq 5\%$) (Fig. 2a). Washing with additional 4 M HCl (f15-f17, 30 mL) eluted residual Sc quantitatively. The only radionuclidic impurity that was detectable in this fraction was ^{56}Co . Fine purification of the ^{44}Ti product from the 3.6g Sc experiment was carried out in a similar fashion (Fig. 2b), where the load solution contained a significantly higher Sc mass (~ 300 mg).

[Figure 2 a&b]

After radiometric analysis, fractions were combined and evaporated to near dryness for further ^{44}Ti separation from ^{56}Co .

4.5 Separation of ^{44}Ti from ^{56}Co

The combined loading effluent contained more than 30% of ^{44}Ti and no detectable ^{56}Co . Further elution with 8 M HCl (35 mL) contained the remaining amount of ^{44}Ti . Recovery yield for ^{44}Ti was $\geq 99\%$, and no ^{56}Co was detected.

5. Discussion

Scandium metal was chosen over scandium oxide or chloride owing to its high thermal and radiation stability. Metal targets also provide a higher ^{44}Ti product yield per target mass. Considering the uncertainty range of the underlying cross sections [22] and a non-Gaussian proton energy distribution in the Sc target body (as discussed previously [38]), the LANL experimental ^{44}Ti physical yield of 150 MBq (4.05 mCi) corresponded quantitatively to the projected thick target yields as calculated on the basis of the underlying $^{45}\text{Sc}(p,2n)^{44}\text{Ti}$ excitation function [19]. This affirmed that the computed production proton energy windows (compare Table 2) represented prevailing energy degradation in the Sc target body. It also proved that no product losses occurred on account of diffusion or evaporation during proton irradiation. The BNL measured yield of 21.8 MBq (0.59) mCi corresponds to 71.1% of the theoretical yield and appears low. The reason for this could lie in a possible entrance energy discrepancy or proton beam attenuation (estimated 17%). The much lower ^{56}Co content at BLIP compared to IPF is due to the higher exit energy from the Sc target at BNL (20.9 MeV). This suppressed the coproduction of ^{56}Co , since the $^{56}\text{Fe}(p,n)$ reaction cross section maximum (436 mb) is at approximately 13 MeV [cf. 18], while the beam degrades to zero in the Sc target used in IPF. It was found that both the LANL and the BNL target had not melted during the irradiation, which was indicative of an adequate thermal contact between target disk and encapsulation.

312 The radiochemical separation of ^{44}Ti from irradiated scandium does not require rapid chemistry
313 due to the long half-life of ^{44}Ti ($t_{1/2}$ 60.0 a). On the other hand, any efficient separation strategy
314 should minimize losses of valuable ^{44}Ti . Based on these two premises, we developed a separation
315 methodology employing a sequence of anion exchange and cation exchange. In a previously
316 published method, cation exchange in hydrochloric acid media was employed [31] where the
317 bulk mass of Sc is retained on the exchange column, while ^{44}Ti is allowed to remain in the
318 mobile phase. This works well for smaller Sc masses (up to a few grams), but becomes
319 suboptimal with larger Sc masses since it requires large column capacities and thus large
320 amounts of resins.

321
322 Other separation modes were evaluated for the purpose of bulk scandium mass removal
323 (“debulking”), including liquid-liquid chromatography, ion exchange and solid phase extraction.
324 The most convenient and efficient method appears to be the application of anion exchange in
325 concentrated HCl media. This method was reported earlier [32] for the isolation of ^{44}Ti from Sc
326 targets for astrophysics purposes. The same approach, however, does not result in a Ti/Sc
327 separation factor as desirable bulk ^{44}Ti production.

328
329 We thus developed a method that combines two previously reported methods. In the first step,
330 the bulk mass of Sc was removed via ^{44}Ti sorption on an anion exchange column in concentrated
331 HCl while the bulk scandium mass eluted (cf. Ref [32], separation factor $\sim 10^2$) (Fig. 3).
332 Titanium-44 was then eluted from the anion exchange column with 4 M HCl at the first sign of
333 breakthrough. The resultant eluent was then directly loaded on a cation exchange column, where
334 ^{44}Ti eluted without sorption while residual Sc mass -which had been considerably reduced from

the original target mass at that point- was strongly retained on the column. This second step imparts in an additional Ti/Sc separation factor of at least 10^4 . Depending on end user requirements, more fine purification steps could be included in the process. All steps were designed to be performed in sequence, without matrix re-constitution or matrix change. Additionally, a third exchange column for the removal of ^{56}Co was tested and can be implemented as needed.

The stable impurities present in the final batch were measured by ICP-OES. Trace (ppm) quantities of copper (302 ± 30), nickel (70.6 ± 7.0), manganese (2.4 ± 0.2) and iron (49.1 ± 5.0) were detected. The effect of these impurities on the final product is dependent on the generator concept and chelate utilized. Once loaded onto an applicable solid generator phase and with repeated use of the generator, the amount of these impurities will likely decrease and their impact minimalized. Future work studying the long term use of a generator concept will determine the true impact of these metallic impurities over time.

The separation tandem introduced in this work is suitable for the processing of comparatively large quantities of scandium (10-30 g). It features both high recovery yields and elevated separation factors. One of the shortfalls, however, is the requirement of concentrated hydrochloric acid (≥ 11.7 M) with the first anion exchange step giving rise to metal equipment corrosion in the hot cell. Moreover, a large excess of concentrated aqueous HCl or the addition of anhydrous HCl in the form of the gas derived from a cylinder is needed to keep the HCl close to saturation. Thus, alternative methods that make use of solid phase extraction chromatography for ^{44}Ti sorption are being explored.

[Figure 3]

Conclusion

We report the production of a significant quantity of ^{44}Ti (175 MBq (4.7 mCi)) via proton irradiation of scandium targets at the proton accelerator facilities LANL and BNL for the purpose of $^{44}\text{Ti}/^{44\text{g}}\text{Sc}$ generator manufacturing. A $^{44}\text{Ti}/^{44\text{g}}\text{Sc}$ generator can supply the PET imaging isotope $^{44\text{g}}\text{Sc}$ (half-life 3.97 h) on a daily basis. An efficient and convenient procedure for the recovery of no-carrier-added ^{44}Ti from 17 and 27 grams of Sc is introduced. This procedure comprises three steps: first, a coarse separation of ^{44}Ti by anion exchange in concentrated HCl with a Ti/Sc separation factor of 10^2 - 10^3 ; second, a cation exchange in HCl media for ^{44}Ti fine purification from residual Sc mass; and, third, employing anion exchange to separate cobalt radioisotopes that originate from the proton activation of Fe and Ni impurities in the Sc target. In summary, this method yielded a 90-97% ^{44}Ti recovery with an overall Ti/Sc separation factor of $\geq 10^6$. Recovered ^{44}Ti will be utilized for the manufacturing of a $^{44}\text{Ti}/^{44}\text{Sc}$ generator [cf. Ref. 34] based upon the high chemical and radionuclidic purity of the isolated product. Future work will focus on further $^{44}\text{Ti}/^{44\text{g}}\text{Sc}$ generator development including longer-term generator performance studies.

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 530

530 **Table 1.**
 531 Maximum nuclear reaction cross sections for the production of $^{44\text{g}}\text{Sc}$.
 532

Nuclear pathway	σ^{max} (mb) at E_p (MeV)
$^{44}\text{Ca}(\text{p},\text{n})^{44\text{g}}\text{Sc}$	735 at 11.3 [18]
$^{44}\text{Ca}(\text{p},\text{n})^{44\text{m}}\text{Sc}$	54 at 13.5 [18]
$^{45}\text{Sc}(\text{p},2\text{n})^{44\text{r}}\text{Ti}(60.0\text{ a})\rightarrow^{44\text{g}}\text{Sc}$	40.3 at 24.1 [19]; 63 at 30 [20]
$^{44}\text{Ca}(\text{d},2\text{n})^{44\text{g}}\text{Sc}$	538.5 at 14.9 [23]
$^{44}\text{Ca}(\text{d},2\text{n})^{44\text{m}}\text{Sc}$	184.5 at 17.3 [23]

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535 **Table 2.**

536 Summary of irradiation parameters pertaining to this study.

537

Target	Sc disk size d×h, mm	Calculated Energy window [MeV]	Beam current incident (on target) [μA]	Accumulated charge [mAh]	Expected thick target yield* [MBq(mCi)]
LANL	50.8 × 5.1	29.6 → 0	230 (220.8)	41.8	145.4 (3.9)
BNL	60.3×1.5	27.3→20.9	111.7 (92.7)	18.3	30.7 (0.83)

538 *The expected thick target yield was calculated using the activation equation [36]. The thin yield
539 curve based on cross sections was integrated over the given energy range; MCNPX-calculated
540 attenuation (proton fluence mesh tallies, comp. Refs. [37,38]) of the beam current during
541 degradation from 116.8→27.3 MeV was ~83% (BNL) and ~96% (LANL).

542

542

543 **Table 3.**544 Product radionuclide activities found in Sc targets after proton irradiation (nuclear data taken
545 from [1]).

546

Radionuclide	Half-life	Activity at EOB [MBq(mCi)]		⁴⁴ Ti thick target yield [%]	
		LANL	BNL	LANL	BNL
⁴⁴ Ti	60.0 a	150 ± 11 (4.05 ± 0.30)	21.8 ± 1.2 (0.59±0.03)	103.2	71.1
⁴⁶ Sc	83.79 d	63719 ± 5735 (1722 ± 155)	11395 ± 683 (308 ± 18)		
⁵⁶ Co	77.27 d	125 ± 8 (3.38 ± 0.22)	none detected		

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Table 4.550 Distribution of ^{44}Ti and $^{46,44\text{m,g}}\text{Sc}$ in the fractions of the large column process.

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	Resin bed volumes [mL]	Eluent	^{44}Ti	$^{46,44\text{m,g}}\text{Sc}$
Load	2.1	12.3 HCl	n/d	52.4%
Wash	2.1	12.3 HCl	n/d	45.0%
Elution	2.5	8.0 HCl	90.0%	0.09%

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553

554 **Figure legend:**

555 **Figure 1.** Titanium-44/ 1 g Sc separation profile obtained for the 15 mL resin bed anion
556 exchanger column.

557 **Figure 2.** Elution curves for ^{44}Ti purification from a) 10 mg of Sc on a 10 mL resin bed cation
558 exchange in 4M HCl and b) 300 mg of Sc on a 17 mL resin bed cation exchange in 1M HCl.

559

560 **Figure 3.** Schematic of the ^{44}Ti separation and purification method developed in this study
561 depicting the three ion exchange column modules: ^{44}Ti retention, trace Sc retention and (if
562 needed) Co retention.
563

Bulk Sc, ^{44}Ti , ^{56}Co in 12 M HCl