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M. Phipps

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^{48}Ca(p,pn)^{47}Ca linac production for the preparation of a ^{47}Ca/^{47}Sc generator

Michael D. Phipps, Pavithra H.A. Kankanamalage, Wilson Lin, Richard E. Darienzo, Lisa Muench, Christopher Vitkun, Dmitri G. Medvedev, Cathy S. Cutler *

Isotope Research and Production Department, Brookhaven National Laboratory, Upton, NY, 11973, US

A B S T R A C T

The production of ^{47}Sc via the nuclear reaction ^{48}Ca(p,pn)^{47}Ca→(β-, $T_{1/2}$ = 4.54 d)^{47}Sc and the assembly of a^{47}Ca/^{47}Sc generator system has been investigated at Brookhaven National Laboratory. To produce ^{47}Ca, a pressed $^{nat}CaCl_2$ target was irradiated with a proton beam at energy on target of 27.5 MeV at Brookhaven Linac Isotope Producer. Irradiated targets were dissolved in water and then acidified with concentrated HCl before separation using extraction chromatography through a diglycolamide (DGA) resin column. After ingrowth, ^{47}Sc was collected at >90 % with low contamination from both nonradioactive metals and coproduced radionuclides. A total of four ^{47}Ca/^{47}Sc separations were performed with 6–7 days between the irradiation and the separation to allow the equilibration of the ingrowing ^{47}Sc.

1. Introduction

A desire for the development of an expanded library of radiopharmaceuticals has prompted interest in the production of therapeutic α and β^- emitting radionuclides. One such candidate radionuclide is ^{47}Sc ($t_{1/2}$ = 3.35 d, $I_{\beta-}$ = 100 %, $E_{\beta max}$ = 0.6 MeV, I_γ = 68 %, E_γ = 159 keV), which has suitable emission characteristics for potential use in targeted beta therapy as well as single photon emission computed tomography (SPECT) imaging from its beta and gamma emissions, respectively (Müller et al., 2014, 2018; Siwowska et al., 2019). Radioisotope ^{47}Sc can be produced from neutron, proton, and photonuclear reactions from ^{48}Ca, ^{50}Ti, and ^{nat}V targets(Deilami-nezhad et al., 2016; Domnanich et al., 2017; Kankanamalage et al., 2023; Mamtimin et al., 2015; Rane et al., 2015; Rotsch et al., 2018). Despite several possible production routes with various target materials, the availability of ^{47}Sc remains limited due in part to limitations from each of the production methods, those being low cross sections, contamination from coproduced radionuclides, or difficult processing chemistry. Neutron production of ^{47}Ca via the ^{46}Ca(n,γ)^{47}Ca reaction requires enriched ^{46}Ca, which is difficult to procure as well as being prohibitively expensive due to the high levels of enrichment required. A photon irradiation production route via the ^{48}Ca(γ,n)^{47}Ca reaction is also possible(Masumoto et al., 1978; O'Keefe et al., 1987; Tompkins et al., 2011). The ^{48}Ca(p, pn)^{47}Ca reaction is investigated in this work for the development of a^{47}Ca/^{47}Sc generator system, which takes advantage of repeated collections of in-grown ^{47}Sc from the decay of ^{47}Ca every 2–3 weeks. A few different separation methods for a^{47}Ca/^{47}Sc generator system have been investigated, and the use of extraction chromatography with diglycolamide (DGA) resin for separation results in high yields and purity of ^{47}Sc(Domnanich et al., 2017; Horwitz et al., 2005; Pawlak et al., 2019; Pourmand and Dauphas, 2010). The style of generator presented here is a reverse of the typical method for chromatography based radionuclide generators. Typically, a radionuclide has a parent isotope bound to a solid support such as a resin, and the desired daughter radionuclide is eluted from the generator at timepoints corresponding to maximum ingrowth of the daughter (Dash and Chakravarty, 2019). In the method described here, the desired daughter is captured on a resin while the parent nuclide and impurities pass through, and the purified daughter is eluted afterwards. The solution containing the parent is then kept and set aside to maximize ingrowth of the daughter before repeating the separation on another DGA column.

2. Materials and methods

2.1. Targetry and irradiation

A pellet was produced via a hydraulic pressing of $CaCl_2$•$2H_2O$ (Sigma Aldrich, Saint Louis, MO) with a 2.375-inch (6.033 cm) diameter die. In a typical experiment ~40 g of powder was poured into a stainless-steel pressing die set and then pressed with 70 tons of force for about

* Corresponding author.
E-mail address: ccutler@bnl.gov (C.S. Cutler).

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Table 1
Physical dimensions of targets and irradiation experiments.

Exp	Target ID	Mass, g	Thickness, inch (cm)	Energy on the salt, MeV	Beam current, μA	Beam on target, h
1	CER	22.17	0.180 (0.457)	23.5	122.23	93.60
2	CES (failed)	20.70	0.180 (0.457)	23.5	122.88	94.76
3	CET	22.10	0.189 (0.480)	22.2	101.95	102.21

1–2 min. The resulting pressed pellet was heated overnight at 650 °C in a high temperature oven, followed by an additional overnight heating at 250 °C. The face of a sintered pellet was sanded and sealed into an Inconel 625 alloy can 0.220 in thick (Table 1). The target was irradiated at the Brookhaven Linac Isotope Producer (BLIP) with an incident of energy 117 MeV with a beam raster consisting of 10 consecutive beam pulses at a radius of 11.5 mm followed by one pulse at 5 mm. Before reaching the target, the proton beam traveled through beamline windows, water layers, and other isotope production targets. The incident energy degradation was calculated to be 27.5 MeV using SRIM software (Ziegler et al., 2010). The irradiated target was allowed to decay for 36 h before opening and processing to allow for short lived radionuclides to decay away and reduce the dose produced by the target. A total of 3 targets were manufactured using the above technique (Table 1).

2.2. Target dissolution

After irradiation, the target was transferred into a shielded enclosure (hot cell), cut open by removing one of the windows, and dissolved in 120 mL DI water with stirring for 2 h at room temperature. After 2 h, 40 mL concentrated HCl (Optima grade) was added to the target solution to complete dissolution and produce a target solution at 3 M HCl concentration.

2.3. Chemical processing

Chemical processing of the irradiated target was carried out in shielded enclosures using manipulators. To arrive at a pure ^{47}Sc product, the following separation strategy was employed: initially, the scandium fraction was separated using DGA resin (Eichrom, Lisli, IL) to remove all Sc isotopes produced in irradiation. Further, the target material was collected and stored to allow ^{47}Sc to in-grow from ^{47}Ca. The in-grown ^{47}Sc was separated again. Columns were packed using 0.25–1.5 g Eichrom DGA resin. Column bed volume was decreased with each subsequent separation to elute ^{47}Sc in smaller volumes as the activity decreased overtime due to decay of ^{47}Ca.

For column preparation, the DGA resin was wetted, packed, and conditioned with 10 mL of 3 M HCl. Columns were then loaded with the dissolved target material in 3 M HCl with approximately 150 mL total volume. The columns were next washed with 10 mL of 3 M HNO_3. Radioscandium was eluted with 0.1 M HCl. Initial, intermediate, and final solutions were assayed by gamma spectroscopy using a High Purity Germanium detector. A precise aliquot was removed from the assayed solution and diluted to the calibrated volume and geometry in a plastic vial. ICP-OES analysis was performed after gamma spectrum analysis.

2.3.1. First separation: removal of scandium fraction produced in beam

The DGA column was prepared by wetting 1.21g of DGA resin in 3 M HCl. The target solution was loaded onto the column 5 h after the target can was opened. The column was washed with 3 M HCl and combined with the load solution (186.3 g). The volume of the total load solution was 157.3 mL. An HPGe sample was prepared from the load solution by taking 100 μL from the sample and diluting it with 2.9 mL of water. The first separation served to remove the radioscandium (^{44m}Sc, ^{48}Sc, ^{47}Sc) that was produced during irradiation. The radioscandium purified in subsequent separations resulted from the decay of ^{47}Ca.

2.3.2. Second separation: first harvesting of in-grown ^{47}Sc

The second separation was performed after 6 d following the first separation to allow for the ingrowth of ^{47}Sc. A new DGA column was packed with 0.51 g of resin to result in a 2 mL column. The column was preconditioned with 10 mL of 3 M HCl before use. The ^{47}Ca solution was passed through the column and was then washed with 2 mL of 3 M HCl and combined with the load solution. The volume of the load solution was 159.0 mL. The column was washed with 3 M HNO_3 (10.7 mL) collected in a different vial. The ^{47}Sc was eluted from the column using 0.1 M HCl (4 x 10 mL fractions).

2.3.3. Third separation: second harvesting of in-grown ^{47}Sc

The third separation was performed 7 d following the previous separation. A new DGA column was packed with 0.2527 g of resin. The column was preconditioned with 10 mL of 3 M HCl before use. The ^{47}Ca solution was passed through the column. The column was washed with 10 mL of 3 M HCl and combined with the load solution. The volume of the load solution was 168.76 mL. The column was washed with 3 M HNO_3 (10.7 mL) collected in a different vial. The ^{47}Sc was eluted from the column using 0.1 M HCl (3 x 10 mL fractions).

2.3.4. Fourth separation: third harvesting of in-grown ^{47}Sc

The fourth separation was performed 8 d following the previous separation. A new DGA column was packed with 0.25 g of resin. The column was preconditioned with 10 mL of 3 M HCl before use. The ^{47}Ca solution was passed through the column. The column was washed with 10 mL of 3 M HCl and combined with the load solution. The volume of the load solution was 175 mL. The column was washed with 3 M HNO_3 (11 mL) collected in a different vial. The ^{47}Sc was eluted from the column using 0.1 M HCl (3 x 10 mL fractions).

2.3.4.1. Gamma spectroscopy. Gamma-ray spectroscopy was carried out using HPGe detector GEM30P4-83 from ORTEC-AMETEK (Oak Ridge, TN, USA) with efficiency of 30 % at 1333 keV relative to NaI detector peak-to-Compton ratio 60:1. The response function determination (energy and efficiency calibration) was performed using standard solution of radionuclides (Eckert and Ziegler, Atlanta, GA, USA) containing ^{241}Am, ^{109}Cd, ^{57}Co, ^{139}Ce, ^{203}Hg, ^{113}Sn, ^{137}Cs, ^{88}Y and ^{60}Co in quantities traceable to National Institute of Standards and Technology (NIST, Gaithersburg, MD, USA). Counting dead time was kept at or below 15 %. Spectra acquisition and analysis was carried out using Gamma Vision Software (version 7.2, AMETEK, Oak Ridge, USA). ^{47}Ca was measured using its gamma rays at 1297.09 keV (67 %) whereas ^{47}Sc was analyzed by its gamma-ray at 159.38 keV (68.3 %). Throughout the separation process, both elements were detected using these gamma energies, with the same standardized geometry as for the calibration of the detector. The material balance for ^{47}Ca and ^{47}Sc was followed by measuring volumes of the starting and intermediate solutions and taking exact aliquots for gamma spectroscopy. The volume was measured using pre-calibrated plastic ware or weight and density for solutions. All the activity values were calculated to end of bombardment (EOB). This method of assay yields the error in the activity measurements at 5–7 %, based on internal validation documentation of this assay method.

2.3.4.2. Elemental analysis. ICP-OES analysis was performed on a PerkinElmer Optima 7300 DV ICP-OES system. 18 MΩ water was used to prepare a 2 % HNO_3 solution that was used to prepare samples for ICP-OES analysis. Calibration solutions were prepared from a standard periodic table mixture. Calibration solutions were prepared at 0.05 ppm, 0.10 ppm, 0.25 ppm, 0.5 ppm, and 1 ppm concentrations of analyte. All samples were analyzed in triplicate with the mean data reported.

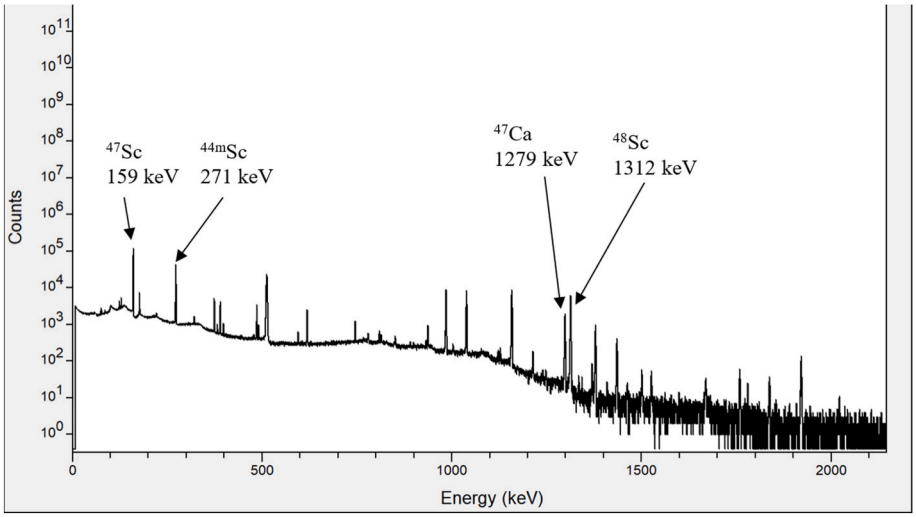

Fig. 1. Gamma spectrum obtained of the dissolved $CaCl_2$ target.

Parameter	ICP-OES
Nebulizer gas flow	0.8 l min^{-1}
Auxiliary gas flow	0.5 l min^{-1}
Plasma gas flow	15 l min^{-1}
ICP RF power	1300 W
Read delay	60 s
Flush at 1 mL min^{-1}	60 s

2.3.5. *Thick target yield estimates for $^{nat}Ca(p,x)^{47}Ca$*

Due to the potential for exploiting $^{nat}Ca(p,x)^{47}Ca$ at higher proton energies, we also performed thick target yield calculations to gauge the viability of this reaction pathway. The physical thick target yield at EOB was calculated using heuristics as outlined by Otuka and Takács (2015). The cross section values were estimated by applying a second order Padé fit to experimentally derived $^{nat}Ca(p,x)^{47}Ca$ cross sections(Faβbender et al., 1999; Michel et al., 1997). Cross section values at ≤7.9 MeV (the threshold energy) were set to 0. Stopping power values were obtained from SRIM software(Ziegler et al., 2010) by assuming protons incident on $CaCl_2$ (density 2.15 g/cm^3). Final reported yields include saturation due to decay. We acknowledge the proton flux will not be constant throughout the $CaCl_2$ target and may reduce calculated yields.

3. Results and discussion

3.1. Targetry and irradiation

The target was dissolved by adding 120 mL of water and stirring for 2 h at room temperature. After a 2 h period, $CaCl_2$ was completely dissolved. The solution was black in color. Concentrated HCl (40 mL, optima grade) was added to the target solution. The solution changed to colorless with some black residue floating around. The target solution volume was determined by mass using 1.05 g/mL as the density for 3 M HCl solution. Next, 20 μL of target solution was taken to make an HPGe sample of the dissolved target (Table 1). The gamma spectrum analysis (see Fig. 1) of the dissolved target solution shows a range of nuclides coproduced due to nuclear reactions with other isotopes of Ca present in ^{nat}Ca as well as Cl present in the $^{nat}CaCl_2$ target material and impurities. The radionuclides produced because of nuclear reactions with ^{48}Ca include ^{48}Sc, ^{47}Sc, and ^{47}Ca. We determined that 1.96 mCi ^{47}Ca was produced in the irradiation. $^{nat}CaCl_2$ was used in the experiment, in which ^{48}Ca has 0.187 % abundance. Higher quantities of produced ^{47}Ca would be expected if enriched $^{48}CaCl_2$ was utilized. Additionally, 8.28 mCi of ^{47}Sc was present in the dissolved target solution. Regarding radioscandium activity, the composition in the target solution was 37 % ^{47}Sc, 32.5 % ^{48}Sc, and 30.5 % ^{44m}Sc. Much of the ^{47}Sc activity came from the competing $^{48}Ca(p,2n)^{47}Sc$ reaction, and was not activity resulting from the decay of ^{47}Ca produced during irradiation. The $^{48}Ca(p,2n)^{47}Sc$ reaction has a higher cross section than the $^{48}Ca(p,pn)^{47}Ca$ reaction over the energy range present during this irradiation. As such, the ^{47}Sc yield from the first separation is not representative of the maximum ingrowth activity of ^{47}Sc from ^{47}Ca in the generator setup.

Table 2
HPGe analysis of the load solution after the first DGA column.

Nuclide	Dilution corrected activity at the EOB (mCi)
^{47}Ca	2.09
^{22}Na	0.00262
^{48}Sc	0.0202
^{44m}Sc	0.0118
^{42}K	2.33
^{43}K	2.65
^{24}Na	0.424
^{57}Ni	1.76
^{52}Mn	0.343
^{51}Cr	0.239
^{58}Co	0.0260
^{55}Co	0.455
^{57}Co	0.0989

3.2. Separations

3.2.1. First separation

The effluent from the separation was colorless. All the black residue from the load solution stayed on the column. Table 2 shows all the isotopes detected by HPGe. Less than 1 % of ^{47}Sc remained in the load solution after passing through the DGA column (see Fig. 2). As other radioisotopes of Sc, including ^{44m}Sc and ^{48}Sc, have the same chemical properties as ^{47}Sc, these were retained on the DGA resin in the first separation and were eluted with ^{47}Sc. The washing steps with 3 M HNO_3 removes non trivalent metals, as well as trivalent transition metals including Fe(III). Bulk Ca from the target and other impurities were washed out, leaving radioscandium bound to the DGA resin before elution with 0.1 M HCl.

3.2.2. Second separation

See Table 3 for ^{47}Sc activity at the time of elution. The total ^{47}Sc activity at the time of elution was 614.5 μCi. ^{48}Sc was used to calculate

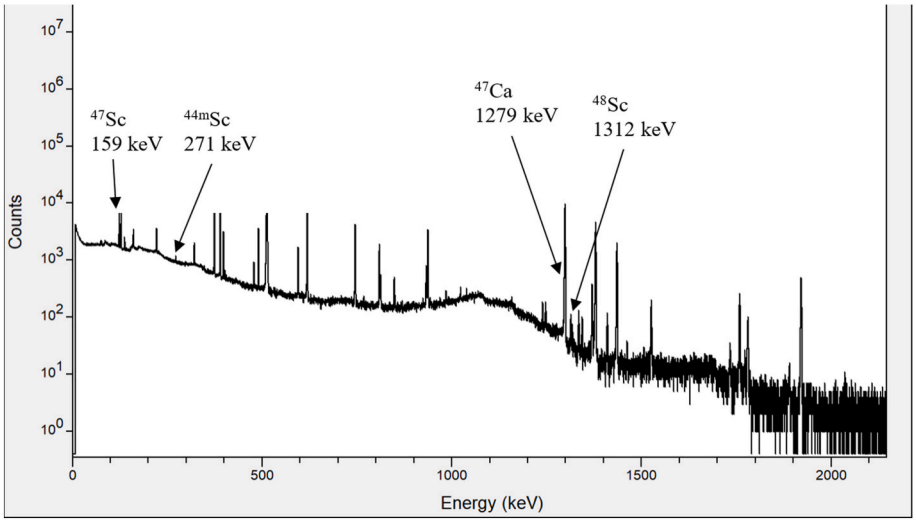

Fig. 2. Gamma spectrum obtained of the load solution after the 1st DGA column. The most relevant peaks to the separation have been annotated.

Table 3
^{47}Sc activity in the second column effluents at the time of elution (* Calculated from the ^{48}Sc in the load solution).

Fraction	^{47}Sc activity (μCi) at the time of elution
Load	51.99*
3 M HNO_3	0.001994
E1	0.04591
E2	555.8
E3	56.55
E4	2.095

the yield of the elution to be 92 % due to the decay of ^{47}Sc by the time of sample counting. ^{48}Sc was not added as a tracer. Although most of the ^{48}Sc was removed in the primary separation, enough remained to be detectable for quantifying the results of the separation with respect to radioscandium. Similarly, the ^{44m}Sc remaining in the solution after the first separation was present in the second separation. This was eluted with the other radioisotopes of Sc in 0.1 M HCl. ^{47}Sc was eluted with 99.8 % radiochemical purity. As can be seen in Fig. 3, no identifiable peak for ^{47}Ca is present in the collected radioscandium eluate. The ICP-OES results from this work (Table 6) shows low impurity from selected nonradioactive metals. The nonradioactive Ca from the bulk target material was eluted with the 3 M HNO_3 washes with little remaining in the collected radioscandium fractions. Other potential metal impurities from the target material or target were low in the collected radioscandium fractions.

3.2.3. *Third separation*

See Table 4 for ^{47}Sc activity at the time of elution. The total ^{47}Sc activity at the time of elution was 242 μCi. ^{47}Sc recovery yield from this column was 94.7 %. ^{47}Sc was eluted with 99.8 % radiochemical purity. The gamma spectrum of the purified radioscandium is shown in Fig. 4. By the third separation, most of the ^{44m}Sc and ^{48}Sc was gone and not detectable unless long count times were performed on the HPGe detector. The decline in the presence of these two radioisotopes of Sc is due

Table 4
^{47}Sc activity in the third column effluents at the time of elution.

Fraction	^{47}Sc Activity (μCi) at the time of elution
Load	13.43
3 M HNO_3	0.05147
E1	0.9509
E2	192.8
E3	47.78

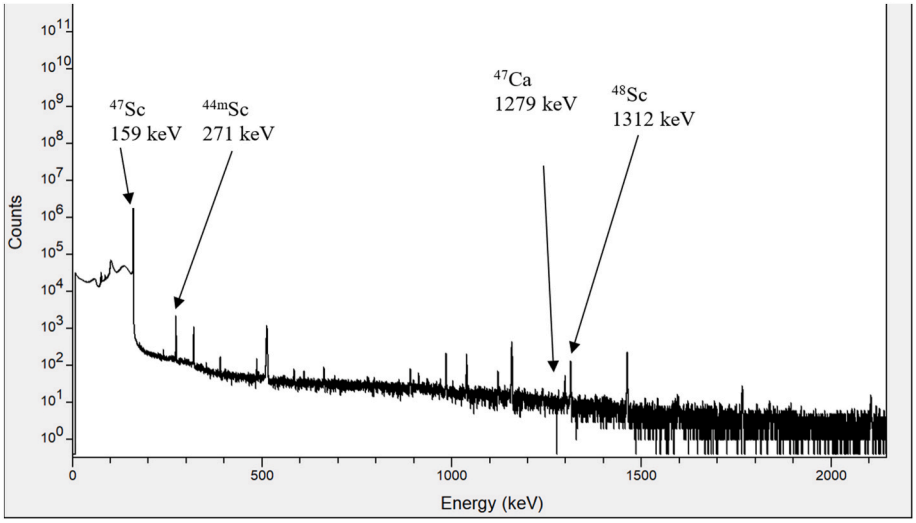

Fig. 3. Gamma spectrum obtained of purified ^{47}Sc after the 2nd DGA column.

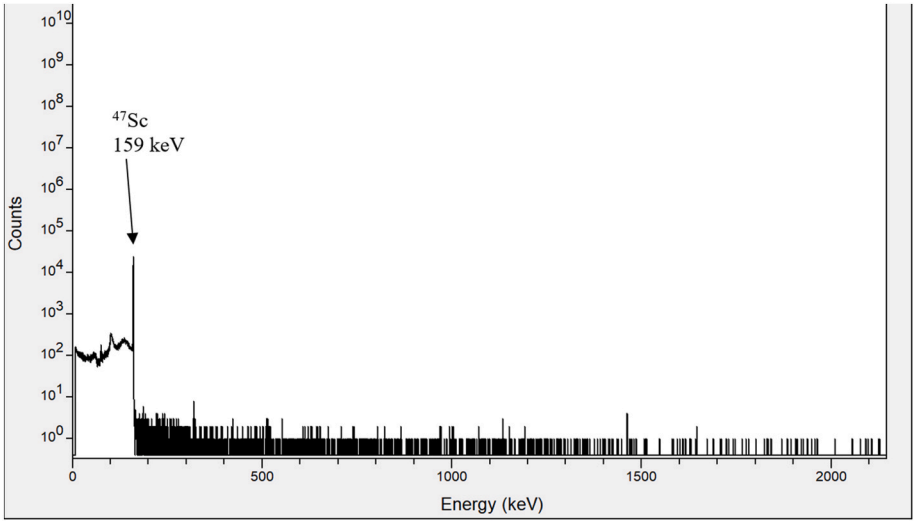

Fig. 4. Gamma spectrum obtained of purified ^{47}Sc after the 3rd DGA column.

Table 5
^{47}Sc activity in the fourth column effluents at the time of elution.

Fraction	^{47}Sc Activity (μCi) at the time of elution
Load	3.471
3 M HNO_3	0.05147
E1	56.10
E2	23.08
E3	0.3567

to their decay as well as removal in the previous separation steps. By contrast, ^{47}Sc continues to grow-in from the decay of ^{47}Ca. The selectivity of the DGA resin for scandium is demonstrated by the reproducible low level of impurities in the 0.1 M HCl fractions from other radionuclides while recycling the load solution between separations. The ICP-OES results from this work (Table 6) show low impurity from selected nonradioactive metals. The nonradioactive Ca and other metal impurities from the bulk target material were washed away in the 3 M HNO_3 washes with little remaining in the collected radioscandium fractions. These results are similar to the ICP-OES results from the previous separation. This is expected due to the recycling of the load solution for each separation. Each load would have similar quantities of nonradioactive metals as they have minimal retention on DGA and simply pass through the column into the load fraction that is collected and recycled.

3.2.4. *Fourth separation*

See Table 5 for ^{47}Sc and ^{47}Ca activity at the time of elution. The total ^{47}Sc activity at the time of elution was 79.6 μCi. ^{47}Sc recovery yield from this column was 95.8 %. ^{47}Sc was eluted with 99.8 % radiochemical purity. As with the previous separations, the efficacy of the DGA separation was again demonstrated. In Fig. 5, the gamma spectrum of the purified radioscandium is shown. Radioisotopes of scandium are the only species identifiable in the gamma spectrum for the purified radioscandium. ^{44m}Sc and ^{48}Sc were nearly fully decayed. The ICP-OES results from this work (Table 6) shows low impurity from selected nonradioactive metals. As in the case of the previous separations, minimal nonradioactive metal impurities were present, and the bulk Ca and other impurities pass through in the load fraction with minimal retention on the DGA resin.

3.2.5. *Generator potential*

Fig. 6 plots the activity curves showing the decay of ^{47}Ca and the ingrowth of ^{47}Sc through their transient equilibrium. Both theoretical

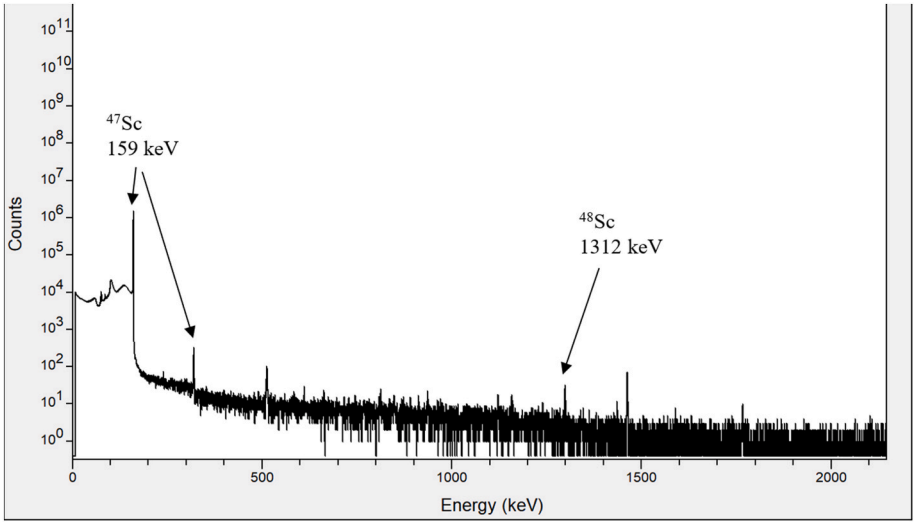

Fig. 5. Gamma spectrum obtained of eluted ^{47}Sc after the 4th DGA column separation.

Table 6
ICP-OES data for all elution samples.

	Mass in the total solution volume (mg)								
	Al	Ca	Cr	Cu	Fe	K	Na	Ni	Pb
Target Solution	0	7628	3.996	0	3.996	11.99	11.99	15.98	3.996
1st DGA Load	1.699	7114	1.699	1.699	0.8495	1.699	1.699	12.74	0.8495
2nd DGA Load	18.03	7000	2.576	2.576	0	0.8587	2.576	12.88	0
2nd DGA E1	0	1.309	0	0.001367	0.000684	0.002051	0.004102	0	0.000684
2nd DGA E2	0.00225	0.50355	0	0.001125	0.0009	0.002025	0.04905	0.000225	0.0009
2nd DGA E3	0.001273	0.01127	0	0.000364	0.000182	0.002545	0.008	0	0.000182
2nd DGA E4	0.00432	0.00936	0	0.00216	0	0.00216	0.0108	0	0.00072
2nd DGA HNO_3 Wash	0.003867	2.049	0.000644	0.08636	0.001933	0.002578	0.005156	0.002578	0.002578
3rd DGA Load	0	6851	1.823	2.734	0	1.823	3.645	11.85	0
3rd DGA E1	0	0.2005	0	0	0	0.009528	0.014292	0.001299	0
3rd DGA E2	0	0.00224	0	0.00004	0.00002	0.00004	0.00022	0	0
3rd DGA E3	0.001713	0.05053	0	0.000856	0.000428	0.001713	0.004282	0	0.000428
3rd DGA HNO_3 Wash	0	0.1982	0	0.001251	0.003126	0.001251	0.003126	0	0.003126
3rd DGA Dry Down Fraction	0.00045	0.06057	0	0.00009	0.00045	0.00153	0.01728	0	0.00054
4th DGA Load	0	6511.05	1.89	2.835	0	1.89	2.835	9.45	0
4th DGA E1	0	1.635	0	0.001878	0.000939	0.002817	0.006573	0	0.000939
4th DGA E2	0	0.1450	0	0.001758	0.001758	0.003515	0.006151	0	0.001758
4th DGA E3	0	0.09681	0	0.001827	0.00274	0.00274	0.006393	0	0.00274
4th DGA HNO_3 Wash	0	0.1075	0	0.001251	0	0.001251	0.001251	0	0
4th DGA Dry Down Fraction	0.00324	1.418	0.00018	0.00027	0.0018	0.00243	0.0405	0.00081	0.00198

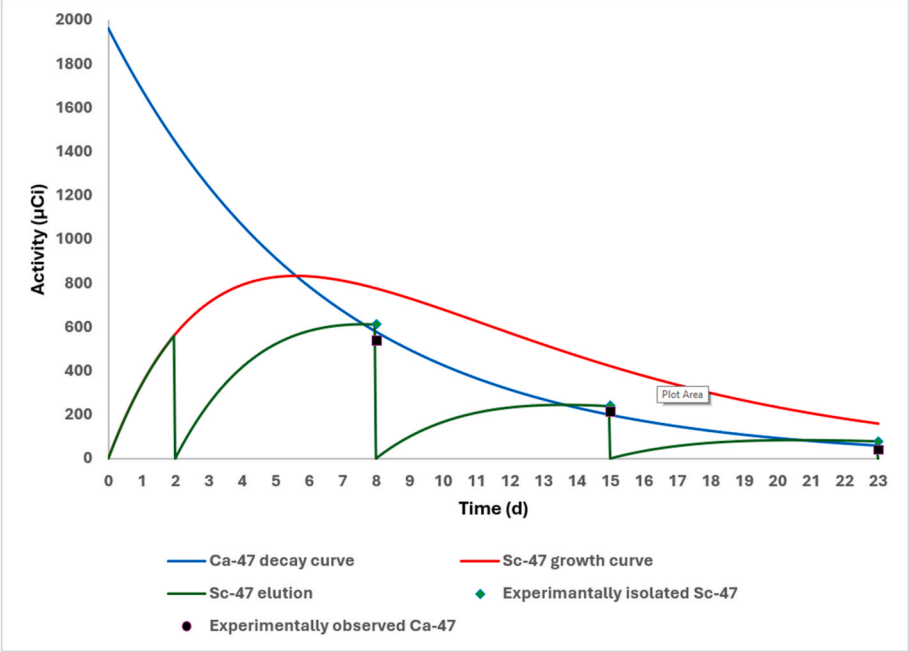

Fig. 6. The theoretical ^{47}Ca decay curve, theoretical ^{47}Sc growth curve, theoretical ^{47}Sc elution curve, experimentally isolated ^{47}Sc, and experimentally isolated ^{47}Ca.

and experimental values for ^{47}Ca and ^{47}Sc are shown. The DGA column size was decreased for each subsequent separation of ^{47}Sc because it was easier to elute ^{47}Sc in a smaller volume since the total ^{47}Sc activity decreased each time. Table 6 describes ICP-OES results for the concentrations of relevant potential stable metal contaminants in the samples. The gamma spectroscopy and ICP-OES (Table 6) data reflect that ^{47}Sc can be recovered with >90 % yield with each elution, and that both radioactive and stable metal contaminants have low breakthrough into the eluted ^{47}Sc fractions in 0.1 M HCl. Other radiometals and stable metals pass through the DGA column in the load in 3 M acid while radioscandium is captured and then eluted with 0.1 M HCl matrix. The greatest contaminant in the eluted ^{47}Sc was from Ca, most likely due to bulk effects as the most abundant metal in the dissolved target. This could be addressed by more thorough washing with 3 M acid before switching to 0.1 M HCl.

This method demonstrates the feasibility of DGA resin to be used in a short-lived generator system using ^{47}Ca to generate ^{47}Sc. Its operation contrasts with the standard design for radionuclide generator systems. Typically, a generator will trap the parent nuclide onto a solid support while the daughter is eluted for use(Dash and Chakravarty, 2019). Here, it is reversed, with the desired daughter being captured on DGA while the parent nuclide and other contaminants pass through with the load, and the daughter being eluted after. One potential advantage that this method offers is lower degradation risk for the solid support due to radiation, since the radioactive material is only interacting with the resin during the separation rather than remaining bound. As may be noted from the plot in Fig. 6, the lifetime of such a generator system would be up to 3 weeks before the ^{47}Ca is decayed to the point of no longer producing appreciable quantities of ^{47}Sc. This places an upper limit on the number of potential doses of ^{47}Sc that could be collected. As mentioned

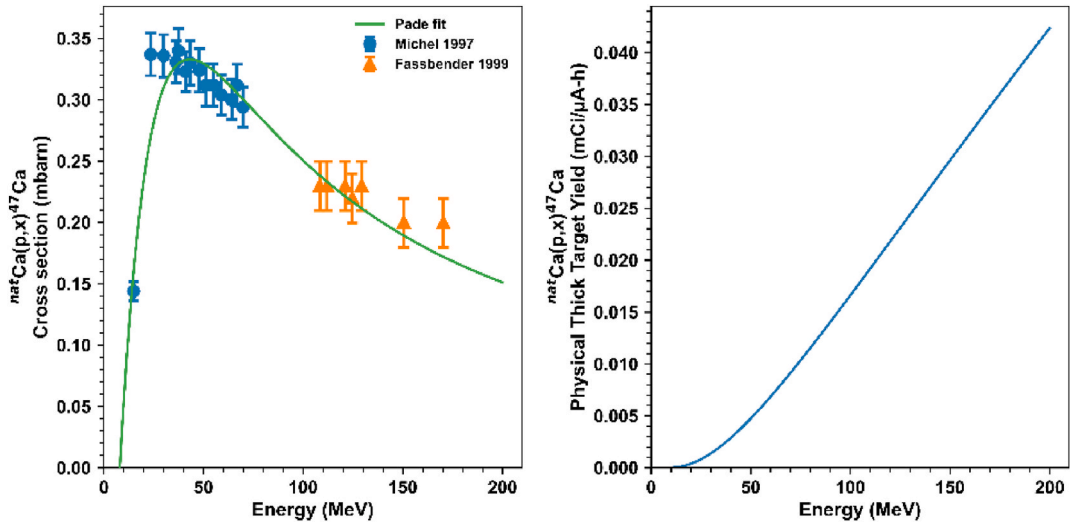

Fig. 7. Pade fit approximation for the $^{nat}Ca(p,x)^{47}Ca$ excitation function (left) and calculated physical thick target yields at EOB for the reaction (right).

by other investigators, the equilibrium time for the ingrowth of ^{47}Sc from ^{47}Ca is approximately 6 d. This combined with the balance of the half-lives between the two radionuclides means that each subsequent collection of ^{47}Sc results in 40 % of the ^{47}Sc activity collected in the previous collection(Pawlak et al., 2019).

Since several radionuclides of interest to the medical community are generally produced at proton energies <100 MeV, the incident 200 MeV protons from BLIP could potentially be exploited to also produce ^{47}Ca by employing $CaCl_2$ as an energy degrader (see Fig. 7). Assuming a proton irradiation current of 165 μA for 4.5 days, and a 10.8 cm thick $CaCl_2$ target to degrade the incident protons from 200 MeV to 100 MeV, the calculated ^{47}Ca activity at EOB is ~330 mCi. Based on the previous discussion, these calculations imply that at least two ~100 mCi and several batches of >40 mCi ^{47}Sc can be distributed for preclinical research. The current lack of facilities producing ^{47}Sc makes this method appealing for providing ^{47}Sc for preclinical or clinical work due to its relatively low cost and simple radiochemical processing.

4. Conclusion

This work demonstrates the production of ^{47}Ca from the $^{48}Ca(p,pn)^{47}Ca$ reaction as well as the feasibility of using the produced ^{47}Ca activity in a $^{47}Ca/^{47}Sc$ generator system. ^{47}Sc can be separated from ^{47}Ca in high yield and with low contamination from nonradioactive metal contaminants.

In future work, further washing will be performed ahead of eluting ^{47}Sc from the DGA resin column. Prepacked resin cartridges may be used due to difficulties with effectively wetting, packing, and conditioning the resin. Radiolabeling will be performed with the activity eluted in future experiments. Future work will also seek to demonstrate the recovery of the $CaCl_2$ target material for target recycling purposes. Targets of enriched $^{48}CaCl_2$ may also be pursued.

CRediT authorship contribution statement

Michael D. Phipps: Writing – review & editing, Writing – original draft, Formal analysis. **Pavithra H.A. Kankanamalage:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Wilson Lin:** Writing – review & editing, Formal analysis. **Richard E. Darienzo:** Writing – review & editing, Investigation, Formal analysis. **Lisa Muench:** Writing – review & editing, Investigation. **Christopher Vitkun:** Writing – review & editing, Investigation, Formal analysis. **Dmitri G. Medvedev:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis. **Cathy S. Cutler:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

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.

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Pavithra H. A. Kankanamalage has since moved to Oak Ridge National Laboratory in Oak Ridge, Tennessee after working on the project discussed in this manuscript. Richard Darienzo has since moved to Stony Brook University Honors College in Stony Brook New York and is also a member of the Institute for Globally Distributed Open Research and Education in Gothenburg, Sweden.

Data availability

Data will be made available on request.

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