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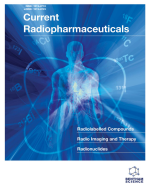
REVIEW ARTICLE



NorthStar Perspectives for Actinium-225 Production at Commercial Scale

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ARTICLE HISTORY

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Abstract: ***Objective:*** Actinium-225, and its daughter Bismuth-213, have great promise in Alpha Immuno Therapy (AIT) for treatment of various disease modalities. Unfortunately, current production levels of actinium-225 do not support broad use of either actinium-225 or bismuth-213 in development or use for disease treatment. Further, the current cost per millicurie is much too high to be sustainable long term. Resolution of both supply and cost issues allows clinical research to proceed through clinical trials and potentially produce one or more effective therapies for cancer or infectious diseases that could benefit the public.

Methods: NorthStar Medical Technologies, LLC, has investigated several routes that could lead to commercial scale production of actinium-225.

Results: This article will discuss those efforts and results to date.

Conclusion: The outlook for future supplies of actinium-225 from multiple sources to support clinical needs is encouraging.

Keywords: ^{225}Ac, actinium-225, ^{213}Bi, bismuth-213, alpha immuno therapy AIT, targeted alpha therapy TAT.

1. INTRODUCTION

With the discovery and proliferation of molecular species that seek out and attach to tumors, new therapies and diagnostics are being developed to enhance the treatment of cancer and other diseases. Some of these molecules have the ability to be conjugated with a radioisotope whereby the radioactivity can be delivered directly to the cells to be treated. Several of today's therapies involve high-energy beta emitters and investigation is underway in the use of alpha particles as the radioisotope. Beta particles are comparatively hundred times more destructive to surrounding good tissue than alpha particles thus providing alpha particles with a potential advantage. Research is potentially showing promise that an even more effective therapy can be developed with alpha emitters - with far less side effects and patient discomfort. Scientists are looking for ways to minimize these side effects of using radioisotopes that produce alpha radiation, which has the benefit of a short destructive path and minimizes damage to adjacent healthy tissue. This technology is commonly referred to as Alpha Immunotherapy (AIT) or Targeted Alpha Therapy (TAT) [1-3].

There are a few alpha emitting radioisotopes with potential for use in alpha therapies. They are: astatine-211, actinium-225, bismuth-213, radium-223 and thorium-227 to name potential candidates. Each of these has it merits and drawbacks as therapeutic alpha emitters but this paper is not intended to address all of those. Each radioisotope does have possible production challenges which this paper attempts to describe some of the efforts conducted to improve the supply of actinium-225 (and its daughter bismuth-213).

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The current worldwide supply of actinium-225 can be summarized as follows:

Oak Ridge National Laboratory (ORNL): Currently produces the bulk of the supply of actinium-225 from a single 150 mCi source of actinium-225's parent, thorium-229 that is milked ~ 8 times per year.

Institute Transuranium Elements (ITU): ITU has a small amount of thorium-229 supplied by Oak Ridge National Laboratory a number of years ago and produces a few hundred millicuries of actinium-225 annually. ITU does not market or sell this actinium-225 but provides it only to their "collaborators".

Russia: There have been various attempts to ship small amounts (few mCi) of actinium-225 from Russia but the actual sources are largely unknown and sporadic in availability [4].

Expanded production at ORNL from the current thorium-229 material is potentially a quick, near-term small but important possible solution. The ORNL source though, even if production is increased, cannot meet the real longer-term therapeutic needs for actinium-225.

All remaining Department of Energy (DOE) controlled thorium-229 is currently part of the uranium-233 stocks held at either Idaho National Laboratory (INL) or ORNL. About 45% of the available thorium-229 was tied up in the Light Water Breeder Reactor (LWBR) fuel pellets. NorthStar has successfully demonstrated through a Cooperative Research and Development Agreement (CRADA) at INL that the technology exists to extract actinium-225 from this source on a routine basis. Unfortunately, DOE has proceeded with the disposal of this source at the Nevada Test Site (NTS). The permanent loss of this source represents the permanent loss of about 45Ci of annual actinium-225 production.

The remaining thorium-229 is part of the high enrichment uranium-233 stored at ORNL. Recovery of this source of thorium-229 would allow for the production of about 60Ci of actinium-225 annually. NorthStar, in conjunction with INL, had proposed to recover a small portion of this thorium-229 using about 1% of the uranium-233 stock, an amount that would produce, in addition to the current production, about 3.6Ci of actinium-225 annually. NorthStar, in collaboration with INL, developed a methodology that would allow for processing this small sample (~15Kg) of uranium-233 within a years' time frame and return it to ORNL for ultimate disposition. Moving this project forward though was complicated by Congressional action in 2005 that removed DOE's flexibility to consider alternative uses, however temporary, of this uranium-233. Demonstration of NorthStar's technology at this scale was consistent with the DOE Office of Inspector General (IG) report [5] relative to having a "demonstrated or proven" process to recover the thorium-229 safely and without impact on the down-blending effort. Assuming this source cannot be accessed, it represents the permanent loss of up to 60Ci of annual actinium-225 production.

Fig. (**1**) [6] demonstrates the importance of actinium-225 supply expansion and clearly indicates that loss of uranium-233 sources means supply expansion can only occur with new production technologies. It also clearly shows that even with access to DOE uranium-233 sources, the approval of multiple treatments using actinium-225 would require alternative production methodologies.

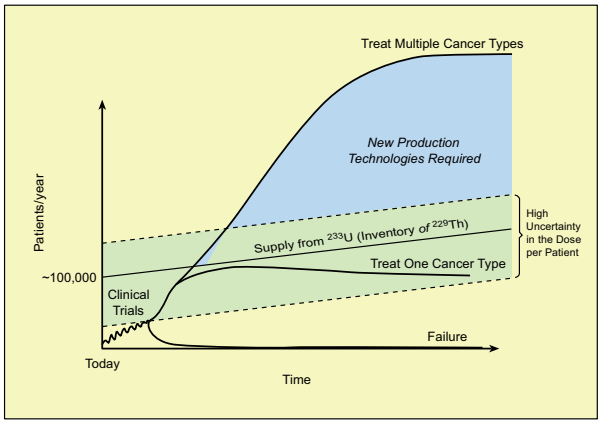

Fig. (1). Relative need of actinium-225 with time.

Most alternative productions have not been fully developed or have only been demonstrated on a small scale and do not produce any meaningful commercially available quantities. Alternative processes being considered rely on either an accelerator based approach (producing radium-225 or actinium-225 directly) or a high-flux reactor to produce radium-225 or thorium-229. Those approaches are:

Using a cyclotron: Ra226(p,2n)Ac225

Using an electron accelerator: Ra226(γ,n)Ra225→Ac225

Using a reactor: Ra226(xn,xβγ)Th229→Ac225

or

Th228(n,γ)Th229→Ac225

or

Ra226(n,2n)Ra225→Ac225

Using a high energy proton accelerator:

Th232(p,spal)Ac225 + Ra225→Ac225

The annual need for actinium-225 has yet to be clearly established as there are no approved treatments using the radioisotope or its daughter bismuth-213. Need will be driven by approvals in the future and varies depending on the radioisotope utilized, *i.e*. actinium-225 or bismuth-213. Based on the amount of effort underway worldwide in TAT [7] the amount of actinium-225 needed annually worldwide in 10+ years could be in the 10's to 100's of Ci range with multiple approvals. One group has estimated the clinical research demand alone could be as high as 50 Ci annually [8].

As an example, one effort reported at the Kanazawa conference [7] by Mark Berger, Joseph Jurcic and David Scheinberg of their acute myeloid leukemia phase 1 trial where the administered doses ranged from 0.5 μCi/kg to 4 μCi/kg of body weight. The MTD (maximum tolerated dose) was reported to be 3 μCi/kg. In a second trial, the doses again ranged from 1 μCi/kg to 4 μCi/kg of body weight but the MTD was not reached. Using the MTD from the phase 1 trial (3 μCi/kg) and assuming standard man weight of 75 kg with 10,000 possible patients per year, an annual actinium-225 need of about 2.3 Ci at the time of administration is calculated. Allowing for at least one half-life of decay (10 days) one could easily see that the at-time of production need is potentially >5 Ci annually to support this one therapy if approved. A second effort reported utilized bismuth-213 for possible treatment of GBM (glioblastoma multiform) and reported an administered dose of 0.3 Ci of bismuth-213 or 1 mCi of actinium-225, noting both were tolerated well.

To meet the potential future need of actinium-225, there have been a number of efforts worldwide not including the NorthStar efforts reported in this article, one NorthStar effort which was previously reported on while still in the planning phase [9]. In the US, the most notable of these is the DOE Tri-Lab effort combining the strengths of three National Laboratories – Los Alamos National Laboratory (LANL), Brookhaven National Laboratory (BNL) and Oak Ridge National Laboratory (ORNL). The Tri-Lab effort takes advantage of the expertise at LANL and BNL in the area of high energy proton accelerators and combines that with the established chemical separation capabilities related to actinium-225 at ORNL. Details of the Tri-Lab efforts are well summarized in a number of presentations and publications [7, 10-12]. This has been a multi-year effort still ongoing to ensure an adequate, reliable supply of actinium-225 [13].

There have been a number of efforts outside the US in Australia, Europe and Russia. In Australia, Melville, *et al*. have reported on both theoretical modeling [14] and a small scale production of radium-225 by photon-induced transmutation of radium-226 [15]. The later article reports the production of 64 μCi of radium-225 with an 18 MeV beam energy electron linac and a dose of 2800 Gy. While small in nature, the results did validate the theoretical calculations. The authors did note that for commercial practicality, a much more powerful electron accelerator would be necessary. They also note the challenge of handling even milligram quantities of radium-226. A later publication [16] by the authors provides further technical details on potential production of actinium-225 in Australia by either use of a high current cyclotron and linear accelerator. Melville and Melville have also reported [17] on the potential of utilizing in-

tense beams of high energy neutrons between the energies of 8 MeV and 12.5 MeV in a fast breeder reactor to produce radium-225.

Apostolidos *et al*. have reported [18] use of a cyclotron to produce actinium-225 via proton irradiation of radium-226. They report maximum yields were obtained at an incident proton energy of 16.8 MeV and that the resulting product was suitable for TAT. The article demonstrated the feasibility of using radium-226, even with its inherent handling challenges, to produce actinium-225. αlfaRim intends to produce actinium-225 by bombarding radium-226 targets in a medium energy cyclotron [8]. They intend to have capability to produce 5 Ci - 10 Ci annually on a predictable schedule using already secured radium-226 stocks. Actinium Pharmaceuticals, Inc [19] (API) has an active multicenter Phase 2 trial underway with their Actimab-A product. API has previously pursued production of actinium-225 also via the cyclotron route and has a patent application covering this method. [20] The effort resulting in the patent describing the separation of actinium-225 from the irradiated radium-226 targets was carried out at the Technical University of Munich (TUM). In 2004, ITM Isotope Technologies Munich was founded and began working with TUM on a number of radioisotope products. Subsequently, in 2007, ITG Isotope Technologies was founded to develop and produce medical radioisotope products, one of which is an actinium-225/bismuth-213 generator offering [21].

There has been significant efforts in investigating the production of actinium-225 in Russia. An effort utilizing an electron accelerator and radium-226 targets to produce actinium-225 has been reported by Maslov *et al.* [22, 23]. Here the authors provide an actinium-225 radiation yield by this method of 550 Bq/(μA·h·mg$_{226Ra}$). They note that irradiation of a 1 gram radium-226 target for up to 150 hours at a beam current of 500 μA and beam energy of 50 MeV could yield 1 Ci of actinium-225. Further, they point out from the experimental results after purification of the resulting actinium-225 that the amount of actinium-227 by activity in the actinium-225 fraction is many orders of magnitude lower thus removing the concern of actinium-227 contamination of the actinium-225 product. Kotovswkii *et al.* [24]. have described a chemical separation and purification of actinium-225 and radium-225 from thorium-229 that yields actinium-225 suitable for TAT. The described separation makes use of both anion and cation resins in a sequential manner to affect the separation with the necessary product purity. Zhuikov *et al* [25]. have irradiated natural thorium foils with 90 MeV, 110 MeV, and 135 MeV protons to demonstrate the production of both actinium-225 and radium-223. These authors report cumulative production cross sections for both actinium-225 and thorium-227 (radium-223 precursor) at these respective incident proton energies. The article also reports the chemical separation scheme used which includes both a liquid-liquid extraction step (TOPO or TBP in toluene) followed by use of an extraction chromatographic resin (TRU® resin [26]) in lieu of the traditional anion and/or cation resins. In a related article by Ermolaev *et al.* [27]. cross sections in the range 20 MeV to 141 MeV for proton irradiation of natural thorium targets were reported for actinium-225, actinium-227, thorium-227 and thorium-228 radioisotopes. These authors note that production of actinium-225 with protons in the energy range of 60 MeV to 140 MeV with good yield is possible. They estimate, in this energy range, an actinium-225 production yield of about 2.6 Ci per 10 day irradiation with 100 μA beam current and a 10 day decay period. Further, the impurity from actinium-227 in such an irradiation would be about 0.23%. Other researchers [28-30] have previously reported actinium-225 production *via* irradiation of thorium targets with proton energies up to 800 MeV.

Various efforts over the last 10 years investigated by NorthStar are described in this article.

2. MATERIALS AND METHODS

Of the process approaches discussed above, NorthStar has examined (through direct experimental knowledge) three of these potential sources: recovery of actinium-225 from LWBR fuel pellets/DOE (thorium-229 bearing legacy materials), electron accelerator production of radium-225 and high energy proton spallation to produce both actinium-225 and radium-225.

2.1. Recovery of Actinium-225 from LWBR Fuel Pellets

2.1.1. Description of the LWBR Fuel Pellets

The LWBR fuel pellets were manufactured in the 1960/1970 time frame to support the then US breeder reactor program. These fuel pellets were part of the thorium breeder reactor development and consisted of ~97% thorium-232 and ~3% uranium-233 as thorium oxide (a ceramic oxide, ThO_2). The US breeder reactor program was effectively ended in 1979 by then US President Carter. These fuel pellets had been placed in storage at INL and during the ensuing 30+ years significant thorium-229 buildup (from the decay of uranium-233) had occurred as depicted below (Fig. **2**).

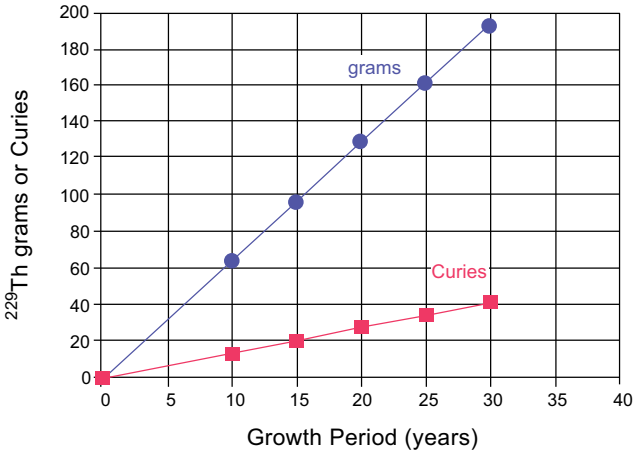

Fig. (2). Amount of thorium-229 in 1.5 metric ton freshly purified uranium-233 as a function of time.

Since these pellets existed and required no further irradiation, the effort was directed to develop a robust chemical separation process that produced a pure actinium-225 product in the end.

2.1.2. Description of the Chemical Process

That chemical separation process developed in 2006 to support that effort is described below. The process is robust

and designed to handle 10's+ of gram quantities of thorium as a starting material.

Fig. (**3**) to Fig. (**7**) present the chemical separation in stepwise flowsheets of the separation that produces, in the end, an actinium product of high purity in a small volume of about 5mL. The UTEVA and DGA resins and cartridges referred to on the flow sheets are standard resin material marketed commercially by Eichrom Technologies, Inc [25]. AGMP-1 is a standard analytical grade macro-porous anion exchange resin commercially available.

Alternatively, one could employ a liquid-liquid separation first step as for thorium masses greater than 50 grams. The liquid-liquid alternative could use Diamyl Amyl Phosphonate (DAAP) in Isopar™ solvent to affect the initial separation from bulk thorium and end with an actinium/radium fraction ready for the second step flowsheet. Fig. (**4**) depicts the second step of the process which provides for the initial separation of the radium and actinium fractions with a secondary purification from residual thorium. Here the actinium and radium fractions are passed thru UTEVA and DGA columns operated sequentially and concurrently to perform three functions:

- Scavenge for traces of thorium (UTEVA),
- Capture actinium (DGA),
- Pass actinium/thorium free radium fraction to collection vessel for subsequent reprocessing for ingrown actinium as desired.

As shown in the initial flowsheet (Fig. **3**) the thorium captured on the UTEVA column, once separated from the DGA column, can be rerouted to the bulk thorium recovered from the AGMP-1 column if it is desired to recover and reuse the thorium at a later date – see Fig. (**5**). The initial actinium-225 fraction from the DGA column in Fig. (**5**) is now ready for final purification (termed "polishing" here).

The final "polishing" of the actinium-225 fraction is demonstrated in Fig. (**6**) to produce a final actinium-225 product that has been subjected to an additional clean-up from thorium (UTEVA) and radium (not collect on either column). Fig. (**7**) is the final flowsheet showing the final product in 5mL of 0.1M HCL. This step can be performed just prior to shipment to attain the purest possible actinium-225 fraction.

Should lanthanide radionuclides be present in the actinium final product an added clean-up step must be added prior to the final polishing (Fig. **7**). That added step is shown in Fig. (**8**). It is clear from the conditions shown in Fig. (**8**) that the lanthanide elements can effectively be removed from the actinium final product using Eichrom Technologies LN resin. Here, the actinium fraction is eluted first while the lanthanides are held up.

2.2. Production of Actinium-225 *Via* Electron Accelerator

2.2.1. Description of the Electron Accelerator Process

An accelerator is a machine that uses an electromagnetic field to accelerate charged particles to a specific energy and contain these accelerated particles (electrons in this case) in a defined beam. The electron accelerator may be linear in nature (Mevex's LINAC) or, in the case specific to IBA Industrial (Rhodotron) a machine that accelerates the electrons in a circular fashion. In either case, the accelerated electrons must be converted to high energy bremsstrahlung by impinging the electrons on a target of sufficiently high Z value to convert the electrons. The converter may be a separate converter plate assembly or the target itself, if useful to do so.

2.2.2. Description of the Process Examined

In a study performed in 1999 by principals of AlphaMed, Inc., a small and relatively simple target assembly was prepared which is shown in Fig. (**9**).

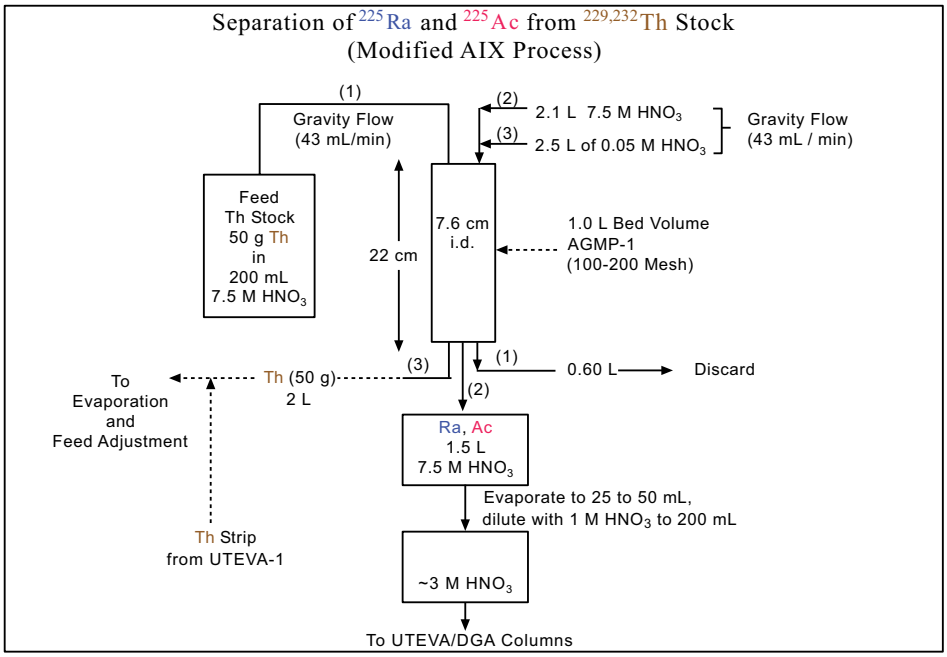

Fig. (3). AIX bulk thorium separation step.

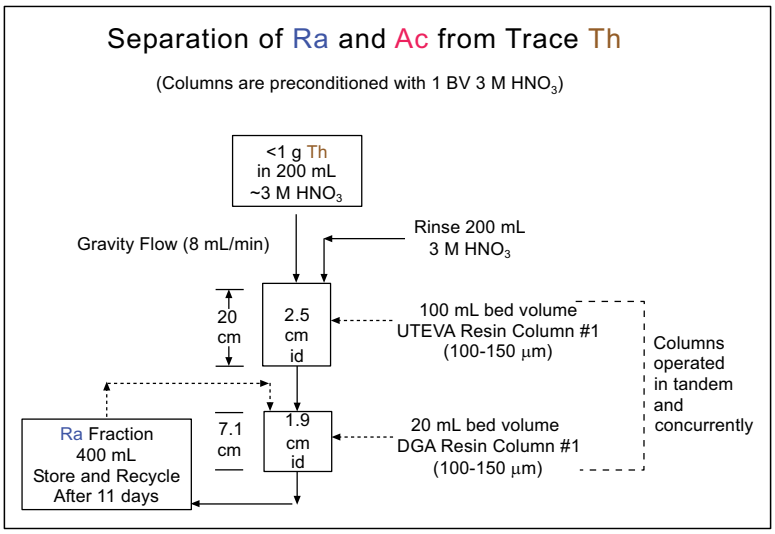

Fig. (4). Initial isolation of actinium and radium fractions with secondary thorium separation.

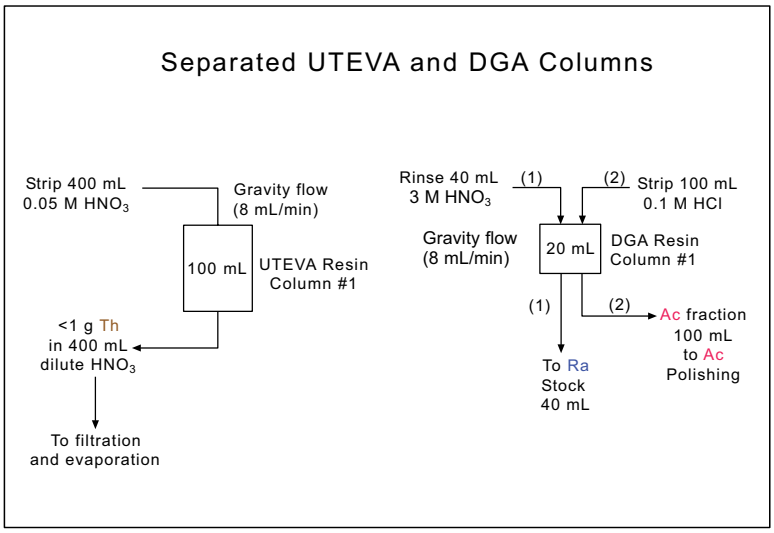

Fig. (5). Recovery of initial actinium fraction and residual thorium if thorium is to be saved.

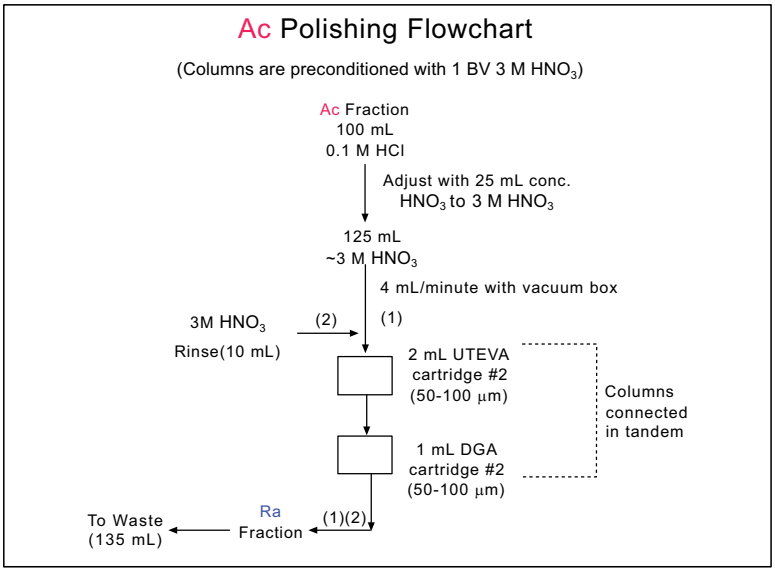

Fig. (6). Step 1 of final actinium purification.

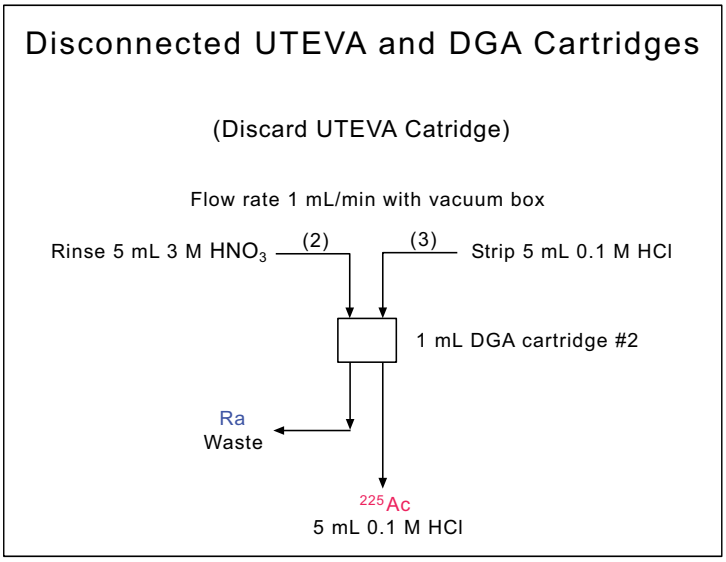

Fig. (7). Final actinium product.

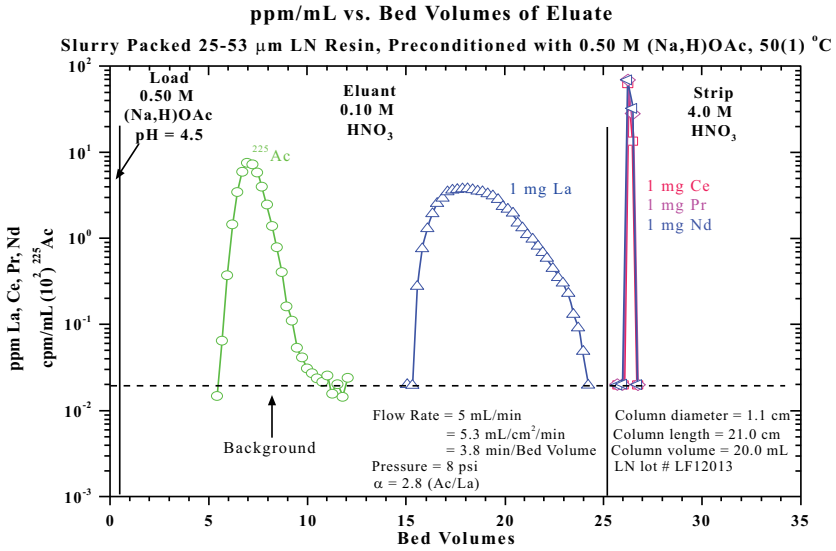

Fig. (8). Added step for removal of lanthanide fission products.

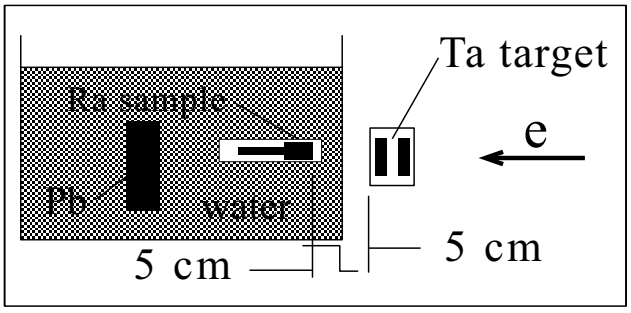

Fig. (9). Drawing of the AlphaMed irradiation assembly.

Here the radium-226 target is exposed to an electron beam of 52 MeV in energy, converted to bremsstrahlung radiation via a tantalum converter plate, which yielded radium-225 from the Ra226(γ,n)Ra225 reaction. The irradiation took place over a three and one-half hour period for a total of 1.4 coulombs of charge. The radium used in this proof-of-concept was provided by the ITU in Karlsruhe, Germany. The irradiated target was return to ITU for processing. Unfortunately, due to logistics issues in shipping the irradiated radium-226 target back to Germany the processed target yielded such a minor amount of material that little could be done with the resulting actinium-225. Nevertheless, this proof-of-concept provided assurance this route was viable though no attempt was made to determine financial feasibility.

2.3. Recovery of Actinium-225 *Via* High Energy Proton Spallation

2.3.1. Description of Spallation Process

As part of previous R&D efforts carried out at Argonne National Laboratory in support of the proposed US Facility for Rare Isotope Beams (FRIB), it was shown that a very effective production mechanism for actinium-225 is spallation of thorium-232 by high energy proton beams. Spallation is a type of nuclear reaction in which a photon or particle hits a nucleus and causes it to emit many other particles or pho-

tons. The higher the energy of the incident particle, the greater the number of fragments produced. High actinium-225 yields are predicted for proton beam energies of 200 MeV and above. At a constant beam current, yields will increase with beam energy to about 400 MeV and then decrease slightly thereafter. While this mechanism can produce the radioisotopes of interest such as actinium-225, the separation of those radioisotopes from spallation targets is not commonly performed, but is being developed by NorthStar and the DOE Tri-Lab effort in the US.

2.3.2. Description of the Target and Mounting

The basic design called for a thorium target 2x1x1 cm^3 (2cm wide, 1cm tall, and 1cm thick). During fabrication of the target a copper enclosure was added and for convenience and simplicity of fabrication and handling of the available thorium sheets, the thorium region of the target was fabricated with dimensions of 0.9x0.4x0.5 in^3 (2.286x1.016x1.27 cm^3) resulting in a total volume of thorium of ~2.95 cm^3. The copper cover that wrapped the thorium was 0.05" (0.127 cm) thick. The overall outer dimensions of the target with enclosure were 1.0x0.5x0.6 in^3 (2.54x1.27x1.52 cm^3), except that the copper plate in the back had a tab making the back copper plate dimensions 1.0x0.75x0.05 in^3 (2.54x1.90x0.127 cm^3). Fig. (**10**) is a picture of the target assembly.

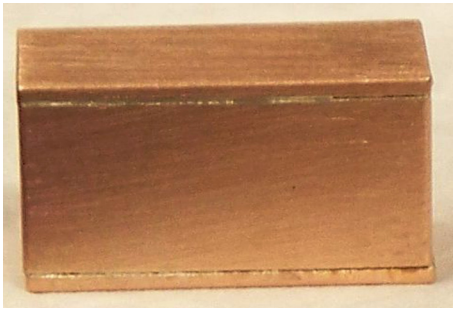

Fig. (10). Target assembly – copper housing with thorium target inside.

Fig. (**11**) shows the target holder mounted in front of the booster beam dump.

Fig. (11). Target holder mounted in front to the 8GeV beam dump of the booster.

2.3.3. Description of the Irradiation

The irradiation of the sample took place in front of the dump for the Fermi National Accelerator Laboratory (FNAL) 8 GeV booster synchrotron. A 400 MeV irradiation position under consideration was ruled out early in the effort as this location is in-vacuum and not preferred by FNAL personnel. Fig. (**12**) is an aerial view of FNAL with an overlay of the FNAL accelerator chain. The booster beam dump location is marked on the figure.

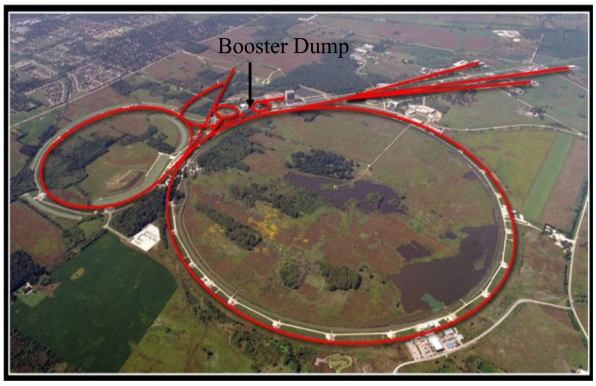

Fig. (12). Fermi National Accelerator Laboratory aerial view.

This location provided an in-air location for the sample that was easily accessible. Dedicated beam could be directed to the sample at an even rate. Additional beam was also received but was just a few percent of the dedicated beam. The desired beam needed was a minimum of 8×10^{16} protons delivered over a period of 2 to 7 days.

The proton beam at FNAL is pulsed and all beam accelerated has a specific purpose. Each pulse is tagged with an event type and all events are loaded into a 10 MHz clock which controls the timing of the beam throughout the accelerator complex. This event type (denoted by a two digit hexadecimal number) specifies the path of the beam, the synchronization of the various accelerators along that path, and the ultimate destination of the beam.

As shown in Table **1**, the primary event used for the irradiation was event 17, a booster study pulse. Other events that end at the booster dump are events, 13, 15, 16, and 1C. The presence of these events was necessary for high energy physics operations and was unavoidable. However, their presence during the irradiation period was benign and they did not significantly affect the cool-down period. Their total contribution was about 4% of the total protons delivered.

A wire scanner upstream of the end of the dump beamline provided profiles of the beam (Figs. **13** and **14**). There was also discoloration on the covering of the opening to the dump. The dimensions of the discoloration are consistent with the profiles from the wire scanner. This strongly indicated that the beam size and positioning is steady. These were then used to determine the size of the sample and the positioning of the sample holder. The sample was sized to the standard deviation of the beam width and height and therefore did not intercept the entire beam. Analysis of the copper cladding provided a measure of the actual number of protons that struck the target.

Event 17 provided beam at a steady rate of approximately 2.5×10^{16} protons per day until the dedicated beam was terminated at 8 AM on June 5. The sample remained in place until 13:30 on June 7 when an access was made to remove the sample. During the two day cool-down period at the end

Table 1. Protons striking the sample by day and event type.

Date	Event 13	Event 15	Event 16	Event 17	Event 1C	Total
June 1	8.79E+12	2.73E+14	3.45E+12	1.05E+16	-	1.07E+16
June 2	1.38E+14	5.39E+14	9.84E+12	2.24E+16	2.86E+13	3.39E+16
June 3	1.98E+14	2.09E+14	6.36E+12	2.56E+16	2.20E+14	6.01E+16
June 4	1.97E+14	5.40E+14	1.13E+13	2.56E+16	-	8.64E+16
June 5 ≤ 8AM	5.24E+13	-	5.74E+12	9.60E+15	-	9.60E+16
June 5 > 8AM	1.24E+14	2.95E+14	4.52E+12	-	-	9.64E+16
June 6	1.65E+14	6.73E+14	8.84E+12	-	-	9.73E+16
June 7	1.15E+14	3.32E+14	6.01E+12	-	-	9.77E+16
Totals	1.00E+15	2.86E+15	5.66E+13	9.36E+16	2.49E+14	

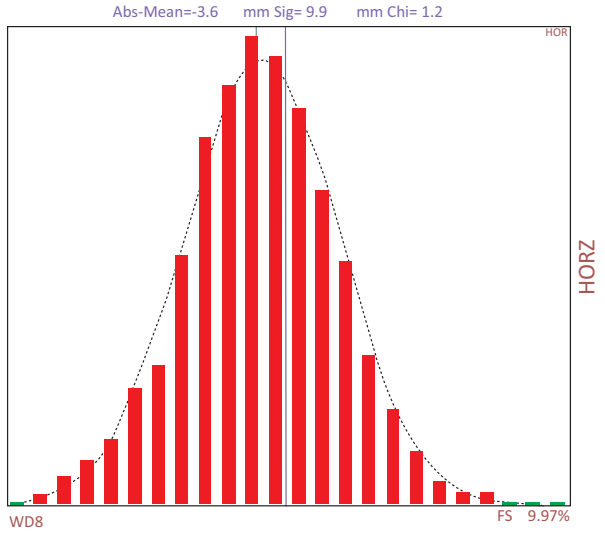

Fig. (13). Horizontal beam profile with a sigma of 1 cm.

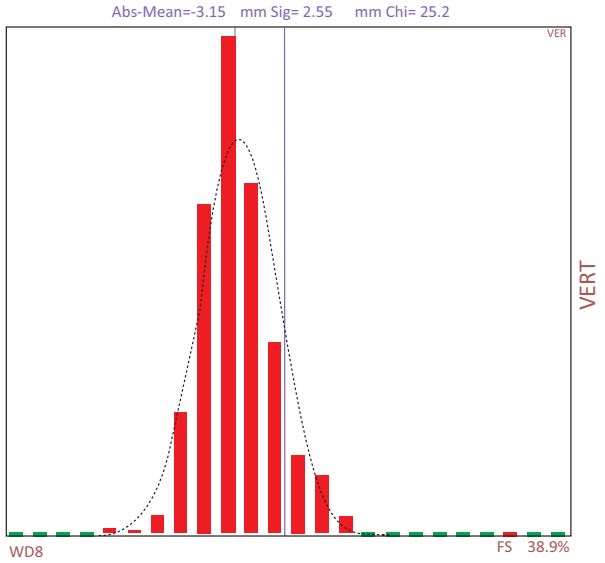

Fig. (14). Vertical beam profile with a sigma of 0.25 cm.

of dedicated irradiations, less than 2% additional beam was delivered to the sample. This irradiation used ~10% of the total protons for ~4 days with the remaining ~90% being used for basic high energy physics research at FNAL.

After the sample was removed from the dump area, it was stored at FNAL until it had cooled to the point that it could be shipped in a shielded shipping container and delivered to Argonne National Laboratory (ANL) for chemical processing.

2.3.4. Analysis of the Beam Profile on the Front Plate

The determination of the beam profile on the front plate during irradiation is important to define the number of protons that hit the plate and as a consequence allowing the calculation of the production cross section of the isotopes of interest, mainly actinium-225.

The irradiation position of the experiment was in front of the dump for FNAL 8 GeV booster synchrotron, as such, it is not a location where the beam positioning and beam profile is closely monitored. During the design activities of the experiment it was decided that the beam profile and beam positioning were to be confirmed by reading the activation of the front copper plate with a gamma collimator, which would allow to read the gamma rays through a small aperture in a tungsten block. The tungsten block was first conceived to shield the gamma-rays coming from other positions in the plate and allowing only the gamma-rays emitted within the collimator line of sight to reach the detector. This allows mapping the gamma spectrum throughout the plate.

The beam profile given by FNAL, based on their previous measurements and supported by the discoloration of the cover at the entrance of beam stop channel, can be approximated by a Gaussian with sigma equals to 1cm. for the horizontal direction and 0.25 cm. for the vertical direction. Using this beam profile it is expected, based on MCNPX calculations, that 65.3% of the protons would hit a 1x2 cm^2 plate placed in the entrance of the beam-stop channel. The calculations performed in support of the design and approval of the experiment wer based on these target dimensions and beam profile. The irradiated target had dimensions, for the area facing the beam in the thorium region of 0.9x0.4 in^2 (2.286x1.016 cm^2).

A new set of calculations was prepared using the dimensions and composition of the irradiated target. As it was described above, in the fabricated and irradiated target, the thorium region had dimensions of 0.9x0.4x0.5 in^3 (2.286x1.016x1.27 cm^3) resulting in a total volume of thorium of ~2.95 cm^3. This can be compared with the 2.0 cm^3 of the original design of the target. The copper cover that wrapped the thorium was 0.05 in (0.127 cm) thick.

It was then decided to perform an analysis of the beam profile on the front plate. Several measurements were taken

at different points on the front plate. The primary approach was to scan the plate in one direction (horizontal) and find the maximum activity in that direction; then scan the direction perpendicular from where the point of maximum activity was found and finally re-scan the first direction at the position of the maximum in the previous direction. The readings obtained are shown in Fig. (**15**) where the values presented are the number of counts for the same period of time read at the positions presented in the figure. Fig. (**16**) presents the horizontal normalized (to the maximum number of counts) Gaussian fitting of the beam profile as it was input in the MCNPX source (solid line) compared with the data read at a few positions along the horizontal line at -0.2cm from the center of the plate. Fig. (**17**) presents the vertical normalized (to the maximum number of counts) Gaussian fitting of the beam profile as it was input in the MCNPX source (solid line) compared with the data read at a few positions along the vertical line at -0.5cm from the center of the plate.

Based on the data the Gaussian distributions for the x and y directions of the beam profile input to the MCNPX source term were as follows:

X-Direction: FWHM = 2.4cm (*vs*. 2.355cm (sigma=1cm) provided by FNAL, center of the distribution = -0.5cm.

Y-Direction: FWHM = 0.6cm (*vs*. 0.589cm (sigma=0.25cm) provided by FNAL, center of the distribution = -0.2cm.

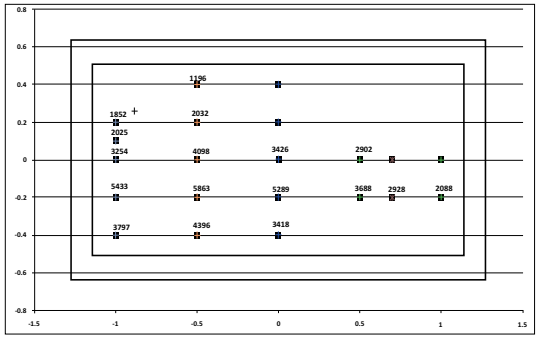

Fig. (15). Number of counts read on the front plate at several positions.

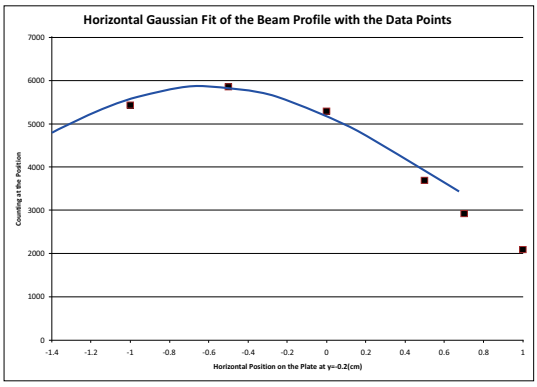

Fig. (16). Gaussian fitting of the counting read (solid line) along the horizontal direction at the line position 0.2cm below the center plate in the vertical direction. The center of the distribution is at -0.5cm from the center of the plate in the horizontal direction. The counting readings are represented by the points in the graph.

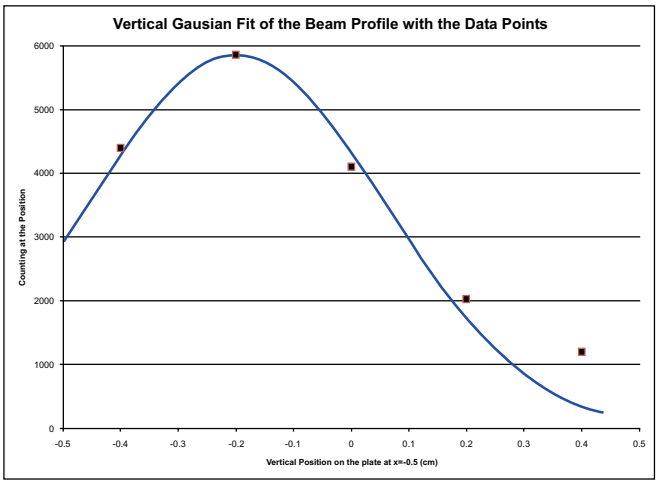

Fig. (17). Gaussian fitting of the counting read (solid line) along the vertical direction at the line position 0.5cm to the left of the center plate in the horizontal direction. The center of the distribution is at -0.2cm from the center of the plate in the vertical direction. The counting readings are represented by the points in the graph.

Thus approximately 70% of the available protons struck the copper target holder with ~60% striking the thorium target.

3. EXPERIMENTAL

3.1. Separation of Actinium-225 from LWBR fuel pellets

A select few LWBR fuel pellets were obtained to be dissolved. Fig. (**18**) shows the pressurized dissolution apparatus ready for use.

Fig. (18). LWBR fuel pellet dissolver.

Fig. (**19**) shows a pellet ready for dissolution with the pressurized dissolution vessel in the background.

Fig. (19). LWBR fuel pellet ready for dissolution.

A total of nine dissolution runs were performed producing just less than 1.5L of dissolved material for the start of the separations process. The dissolved material represented about 250 microcuries of actinium-225. After dissolving the LWBR fuel pellets, the separation scheme described in section 2.1.2 above was followed utilizing the alternative liquid-liquid option for the initial separation of bulk thorium. Lanthanides (mostly lanthanum and cerium) were found to be present in parts per billion (ppb) concentrations verifying that the use of LWBR fuel pellets would require the lanthanide separation addition shown in Fig. (**7**). For comparison, the mass of actinium-225 present is several orders of magnitude lower thus small amounts of lanthanides present could hinder the use of the actinium-225 produced.

3.2. Separation of Actinium-225 from Electron Beam Radium-226 Target

As mentioned above in section 2.2.2, due to logistics difficulties in returning the radium-226 target to ITU, there was little that could be accomplished with the material.

3.3. Separation of Radium-225 and Actinium-225 Spallation Thorium Target

The main objective of the effort was to demonstrate the production of actinium-225 by the spallation of a thick thorium target. In addition to actinium-225, other products are presented in the irradiated thorium target but this analysis will be restricted to a small number of isotopes.

3.3.1. Chemical Separation of Actinium from Thorium Target

The thorium-232 target will contain a mixture of radioisotopes at the end of the irradiation and a robust chemical separation is necessary to purify the actinium isotopes. With a cool-down period of about 10-days, the residual target activity will be reduced significantly due to decay of the shorter-lived isotopes produced during the irradiation. Actinium isotopes present will be actinium-225 and actinium-227 in an activity ratio expected to be about 1000:1. The shorter-lived 1.2-day actinium-226 will have decayed about 3 orders of magnitude by processing time. Fig. (**20**) shows a comparison of the raw dissolved target to the organic and aqueous phases. Note protactinium-233 absence in the aqueous phase.

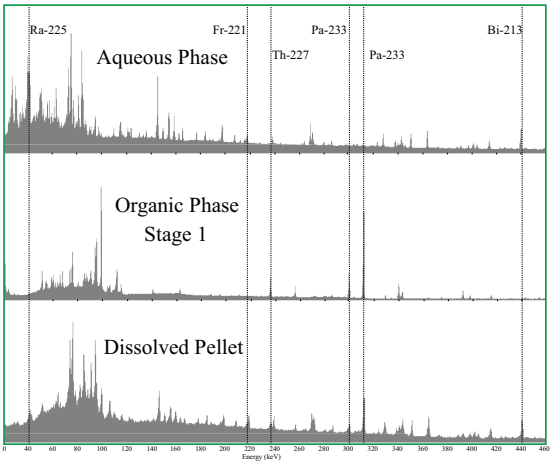

Fig. (20). Gamma spectra of the dissolved target, organic phase and aqueous phase.

Fig. (**21**) is an alpha spectrum comparing the dissolved target solution with the aqueous feed to the first UTEVA/DGA column set (marked IX feed). Here one can see the aqueous feed is mostly devoid of thorium. The purpose of the first UTEVA/DGA column set is to scavenge the remaining thorium and provide the initial capture of the actinium product. This separation also serves as the primary actinium/radium separation. The radium fraction can be saved and used to milk "second chance" (and so forth depending on the actual activity of radium-225 produced) actinium-225.

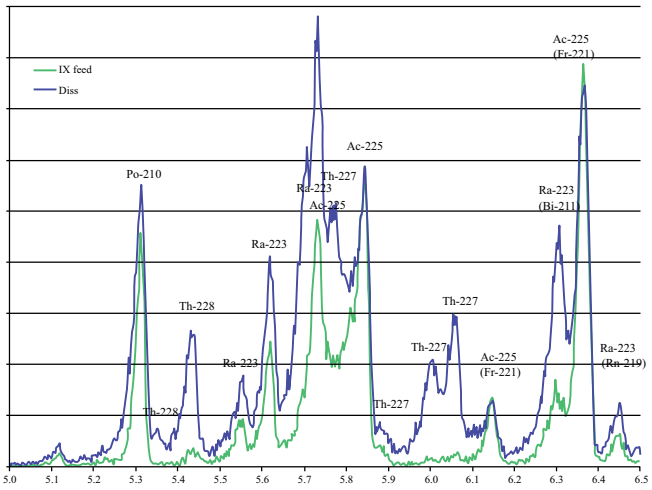

Fig. (21). Initial alpha spectra comparing aqueous feed to the first UTEVA/DGA column with dissolved target solution before initial separation.

Of importance to note at this point is that the directly produced actinium-225 contains a small fraction of actinium-227 (<0.15% EOI). This effort was not designed to address if this small fraction of actinium-227 would interfere with the use of actinium-225 directly as a therapeutic agent. It does not interfere with the use of this actinium-225 to generate bismuth-213 for therapeutic use. Regardless, the separation and setting aside the radium-225 fraction as shown in the initial separation shown in Fig. (**3**) allows for the recovery of "second chance" and so forth actinium-225 that is devoid of actinium-227.

Fig. (**22**) depicts the separation of the aqueous phase feed to the initial UTEVA/DGA ("A") resin separation to the final actinium product. The alpha spectra presented clearly shows the actinium product contains no thorium and no radium, only actinium plus actinium daughters.

As noted above, lanthanide fission products were observed in the gamma spectra but as none are alpha emitters, they do not appear in this slide. The insertion of the separation shown in Fig. (**7**) above is necessary for future production of actinium-225 *via* this method to remove these unwanted radionuclides.

4. RESULTS AND DISCUSSION

4.1. Chemical Separation from LWBR Fuel Pellets Effort

LWBR fuel pellets had been thought to be unusable for producing actinium-225 because its parent, thorium-229, could

Table 2. Activities of actinium and related radioisotopes in millicuries.

	Ac-225	Ac-227	Ra- 225	Th-227	Ra-223
Calculated Activity	2.51	0.004	0.57	0.86	1.22
Measured (±1ϭ TPU)	2.08 ±0.20	0.003+0.00100	0.49±0.11	0. 86±0.11	0.77±0.09

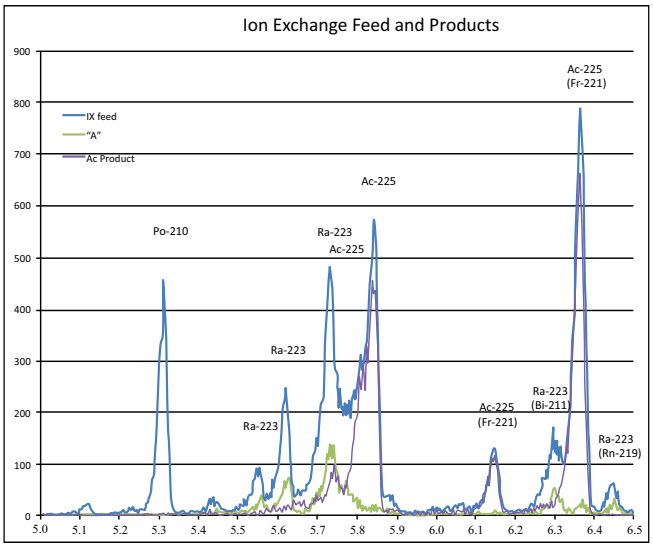

Fig. (22). Comparison of the aqueous feed to the final actinium product.

not be isolated from the bulk thorium-232 of the fuel pellet. The chemical process developed and described above provided an overall recovery of actinium-225 of about 80%. Decontamination factors (DF) from the primary contaminants were:

Thorium isotopes (229 & 232): $>10^{11}$
Uranium-233: $>10^{11}$
Radium: $>10^{8}$
Impurities other than listed above were found to be <<µg/mCi of actinium-225.

About 50 microcuries of the final product was sent to Martin Brechbiel at the National Institute of Health (NIH) but due to delays in shipping and using the material, it could not be extracted from the vial it was shipped in, no analytical tests could be performed.

4.2. Spallation Irradiation Effort

The activity of the irradiated thorium, after separated from the copper enclosure, was measured at several phases of the chemical separation process and adjusted to the EOI (end of irradiation) time (assumed to be June 5th 2011 at 8:00 AM). The reported activity is corrected to the EOI when intense beam irradiation ceased.

Table **2** presents the results of the production of five primary radioisotopes of interest comparing calculated (MCNPX/CINDER) with experimental results. The presented data is the average of the analysis performed by two different laboratories at ANL and at the PG Research Foundation. While slightly lower across the board than the calculated values, the agreement with the predicted activities is good and clearly shows that the calculations can be used to predict yields from the process. This demonstrated predictive ability increases the probability of success as the process in the future.

One can note from Table **2** that the actinium-227 content, by activity, in the actinium-225 is about 0.14% at EOI. Thus at 10 days post EOI, the amount would be about 0.28% which is consistent with previously reported amounts [11, 27].

CONCLUSION

NorthStar's first attempt to provide a solution to the actinium-225 needs concentrated on DOE legacy materials. As those legacy materials are either no longer available (LWBR fuel pellets) or of questionable availability (uranium-233 stocks) for the future, NorthStar no longer is actively working on this pathway. Regardless, if multiple treatments utilizing either actinium-225 or bismuth-213 are approved in the future, DOE legacy materials alone might not have been sufficient.

Production of actinium-225 *via* the electron accelerator route utilizing radium-226 as target material as noted above is a viable route. As NorthStar is pursuing molybdenum-99 production using electron accelerators with beam energies of 40 MeV and beam currents in excess of 500 µA for irradiation periods of similar length, this is a potentially attractive option to the company.

The high energy proton spallation effort also described herein to investigate an alternative production route for actinium-225 that does not utilize any DOE legacy materials derived from uranium-233 was proven successful at the proof-of-principal level. Actinium-225 investigative efforts as a potential therapeutic agent have been hampered by the lack of supply and the high costs of current production methods. The investigation of this production route by multiple entities targets the elimination of both these issues. By demonstrating the potential of the production route, these efforts demonstrate that supply and costs issues plaguing research and clinical development with actinium-225 could be resolved. Resolution of both supply and costs issues would allow clinical research to proceed through clinical trials and potentially produce one or more effective therapies for cancer or infectious diseases that could benefit the public. A host of fission and other spallation product radioisotopes, whose value determination has not been identified, are also co-produced.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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REFERENCES

[1] Kratochwil, C.; Bruchertseifer, F.; Giesel, F.; Weis, M.; Verburg, F. 225Ac-PSMA-617 for PSMA-targeted α-radiation therapy of metastatic castration-resistant prostate cancer. *J. Nucl. Med.*, **2016**, *57*, 1941-1944.

[2] Miederer, M.; Scheinberg, D.; McDevitt, M. Realizing the potential of the Actinium-225 radionuclide generator in targeted alpha particle therapy applications*, Adv. Drug Deliv. Rev.*, **2008**, *60*, 1371-1382.

[3] TM-44815, Alpha emitting radionuclides and radiopharmaceuticals for therapy*,* report of iaea technical meeting, June 24-28, **2013**, Vienna, Austria.

[4] Press Release, Isonics Corporation, isonics begins supplying rare cancer-fighting isotope to national institutes of health, January 5, **2005**.

[5] Special Report, U.S. Departmetn of Energy, Office of Inspector General, Office of Audit Services, Meeting Medical and Research Needs for Isotopes Derived from Uranium-233, DOE/IG-0795, May 29, **2008**.

[6] Forsberg, C.W. Uses for U233, Briefing for USDOE, March 22, **2000**.

[7] 10th International Symposium on Target Alpha Therapy, Ishikawa Ongakudo: Hougaku Hall, Kanazawa, Japan, 30 May -1 June, 2017.

[8] αlfaRim Medical Holding BV, Wassenaar, Netherlands, Available from http://www.alfarim.org/actinium-225/ [Accessed on 1st July].

[9] Harvey, J.; Nolen, J.; Kroc, T.; Gomes, I.; Horwitz, P.; McAlister, D. Production of actinium-225 via high energy proton induced spallation of thorium-232, proceedings of the workshop on applications of high intensity proton accelerators. FermiLab, Chicago, 19-21 October, 2009, R. Raja & S. Mishra, Editors, 321-326.

[10] Radchenko, V.; Engle, J.; Wilson, J.; Maassen, J.; Nortier, F.; Taylor, W.; Birmbaum, E.; Hudston, L.; John, K.; Fassbender, M. Application of ion exchange and extraction chromatography to the separation of actinium from proton-irradiated thorium metal for analytical purposes. *J. Chromatogr. A.*, **2015**, *1380*, 55-63.

[11] Griswold, J.; Medvedev, D.; Engle, J.; Copping, R.; Fitzsimmons, J.; Radchenko, V.; Cooley, J.; Fassbender, M.; Denton, D.; Murphy, K.; Owens, A.; Birnbaum, E.; John, K.; Nortier, F.; Stracener, D.; Heilbronn, L.; Mausner, L.; Mirzadeh, S. Large Scale Accelerator Production of ^{225}Ac: Effective cross sections for 78-192 MeV protons incident on ^{232}Th Targets*, Appl. Radiat. Isot.,* **2016**, *118*, 366-374.

[12] Radchenko, V.; Mastren, T.; Meyer, A.; Ivanov, A.; Bryantsev, V.; Copping, R.; Denton, D.; Engle, J.; Griswold, J.; Murphy, K.; Wilson, J.; Owens, A.; Wyant, L.; Birnbaum, E.; Fitzsimmons, J.; Medvedev, D.; Cutler, C.; Mausner, L.; Nortier, F.; John, K.; Mirzadeh, S.; Fassbender, M. Radiometric evaluation of diglycolamide resins for the chromatographic separation of actinium from fission product lanthanides. *Talanta,* **2017**, *175*, 318-324.

[13] National Isotope Development Center (NIDC) Newsletter, No. 8, February **2016**.

[14] Melville, G.; Liu, S.; Allen, B. A Theoretical model for the production of Ac-225 for cancer therapy by photon-induced transmutation of Ra-226. *Appl. Radiat. Isot.*, **2006**, *64*, 979-988.

[15] Melville, G.; Meriarty, H.; Metcalfe, P.; Knittel, T.; Allen, B. Production of Ac-225 for cancer therapy by photon-induced transmutation of Ra-226. *Appl. Radiat. Isot*., **2007**, *65*, 1014-1022.

[16] Melville, G. and Allen, B. Cyclotron and Linac Produciton of Ac-225. *Appl. Radiat. Isot.*, **2009**, *67*, 549-555.

[17] Melville, G.; Melville, P. A Theoretical model for the production of Ac-225 for cancer therapy by neutron capture transmutation of Ra-226. *Appl. Radiat. Isot.*, **2013**, *72*, 152-157.

[18] Apostolidis, C.; Molinet, R.; McGinley, J.; Abbas, K.; Möllenbeck, J.; Morgenstern, A. Cyclotron production of Ac-225 for target Alpha therapy. *Appl. Radiat. Isot.*, **2005**, *62*, 383-387.

[19] Actinium Pharmaceuticals, Inc., New York, NY, https://www.actiniumpharma.com/about.

[20] U.S. Patent No. 8,715,598, Method for the purification of radium from different sources*,* granted 6 May **2014**.

[21] http://www.isotope-technologies-munich.com/company/about-us/

[22] Maslov, O.; Sabel'nikov, A.; Dmitriev, S. Production of 225Ac in the 226Ra(γ,n) photonuclear Reaction at the electron accelerator - MT-25 microtron. Joint Institute for Nuclear Research (JINR), Report No. JINR-R-12-2004-209, **2004**.

[23] Maslov, O.; Sabel'nikov, A.; Dmitriev, S. Preparation of 225Ac by 226Ra(γ,n) photonuclear reaction on an electron accelerator, MT-25 microtron. *Radiochemistry*, **2006**, *48*, 195-197.

[24] Kotovskii, A.; Nerozin, N.; Prokofiev, I.; Shapovalov, V.; Yakovshchits, Y.; Bolonkin, A.; Dunin, A Isolation of Actinium-225 for Medical Purposes. *Radiochemistry*, **2015**, *57*, 285-291.

[25] Zhuikov, B.; Kalmykov, S.; Ermolaev, S.; Aliev, R.; Kokhanyuk, V.; Matushko, V.; Tananaev, I.; Myasoedov, B. Production of 225Ac and 223Ra by irradiation of Th with accelerated protons. *Radiochemistry*. **2011**, *53*, 73-80.

[26] Eichrom Technologies, Inc., Lisle, IL USA http://www.eichrom.com/

[27] Ermolaev, S.; Zhuikov, B.; Kokhanyuk, V.; Matsuhko, V.; Kalmykov, S.; Aliev, R.; Tananaev, I.; Myasoedov, B. Production of actinium, thorium and radium isotopes from natural thorium irradiated with protons up to 141 MeV, *Radiochim. Acta*, **2012**, *100*, 223-229.

[28] Bonetti, R.; Chiesa C.; Guglielmetti, A. Nuclear structure effects in the exotic decay of 225Ac *via* 14C emission. *Nucl. Phys. A*, **1993**, *562*, 32-40

[29] Moskvin, L.; Tsaritsyna, L. Isolation of actinium and radium from a thorium target irradiated by 600 MeV protons*, At. En.,* **1968**, *24*, 383-384.

[30] Weidner, J.; Mashnik, S.; John, K.; Ballard, B.; Birnbaum. E.; Bitteker, L.; Couture, A.; Fassbender, M.; Gogg, G.; Gritzo, R.; Hemez, F.; Runde, W.; Ullmann, J.; Wolfsberg, L.; Nortier, F. 225Ac and 223Ra Production via 800 MeV proton Irradiation of natural Thorium Target, LANL Report LA-UR-11-07090, Los Alamos **2011**.