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Accelerating Production of Non-Carrier Added Actinium-225 (n.c.a. Ac-225)

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MEDICAL RADIOISOTOPES

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INTRODUCTION

Actinium has a pedigree leading back to the most famous researchers of radioactivity, Marie and Pierre Curie. Actinium was first discovered by Andre Debierne in pitchblende residues left by the Curies in 1899.[1] There remains some controversy around this, however, with some scientists and historians positing that the true discoverer was Friedrich Oskar Giesel.[2]

Ac–225's medical uses were discovered through a "quirk of history" starting in the 1960s, when scientists noticed that stockpiles of uranium isotopes naturally transmute into other elements, eventually converting to thorium–229 (Th–229). In 1994, a very small volume of Ac–225 was "milked" from a Th–229 source and was shipped to the National Cancer Institute.[3] This method of Ac–225 production continues to this day, but only provides a tiny fraction of the potential demand for this radioisotope. It is detailed further in "Method 1" below.

Alpha particles have high decay energy (over 5.9 MeV in the case of Ac–225), which means they can cause fatal double–strand DNA breaks in targeted cells. Another attribute is that they can only travel a short distance in biological tissues, which means that, if placed properly, the particles can kill cancer with radiation and limit damage to surrounding areas. As research continued, more promising results were found. A particularly interesting case study was published in 2016 showing dramatic reduction in tumor spread in a prostate cancer patient (**Figure 1**).[4]

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[1] Wall, G. 2003. *It's Elemental: The Periodic Table – Actinium*. CHEMICAL AND ENGINEERING NEWS. https://tinyurl.com/3m8tpkf2.

[2] Adloff, J–P. 1993. FUNDAMENTALS OF RADIOCHEMISTRY (1st ed). CRC Press. doi:10.1201/9781351072199

[3] Shea, SB. 2018. *The Journey of Actinium–225: How Scientists Discovered a New Way to Produce a Rare Medical Radioisotope. United States* Department of Energy. https://tinyurl.com/4rbv49nw.

[4] Kratochwil, C, Bruchertseifer F, et al. 2016. *^{225}Ac–PSMA–617 for PSMA–Targeted α–Radiation Therapy of Metastatic Castration–Resistant Prostate Cancer.* J NUC MED 57:1941–1944. doi:10.2967/jnumed.116.178673.

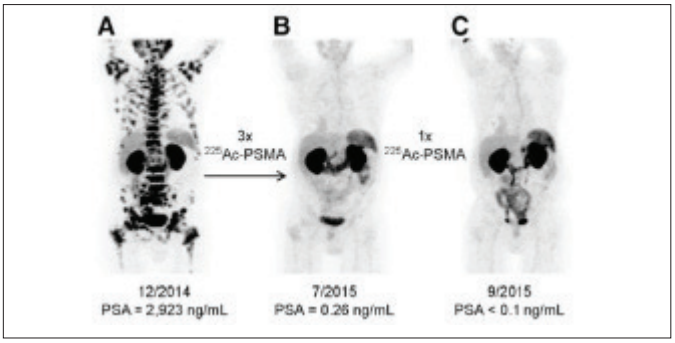

Figure 1. Three images of a patient with end-stage prostate cancer who was treated at the University Hospital Heidelberg. The first was taken before the patient was treated with Ac-225, the second after 3 doses, and the third after 1 additional dose.[5]

The very limited current availability of Ac-225 for clinical applications has necessitated the investigation of alternative production routes.[6] This has encouraged companies, research laboratories, and even the United States government to research new ways to generate economically viable commercial-scale volumes of this precious alpha emitter.

Very small amounts of Ac-225 also have been made in Russia, Germany, Australia,[7] and Japan[8]; however, the isotope has a half-life of 10 days and cannot be stockpiled. Therefore, Ac-225 must be manufactured routinely to create a consistent supply. Exports suffer decay before use, which precludes imported product from being the primary route of supply. A domestic source is therefore essential if patients in the United States are to benefit fully from this promising medical radioisotope.

One other important point to note is that, due to the potency of Ac-225, relatively small quantities are needed for each patient dose. Current data indicates that 200-250 µCi may be an appropriate dose and about 4 treatment cycles per patient. Thus, 1 Ci of Ac-225 could be enough to treat as many as 1000 patients, and 100 Ci enough to treat as many as 100,000 patients.

Clearly, there is a need to find technologies that can be scaled up to produce hundreds of Ci per year. Fortunately, there are several routes for the production of Ac-225 at an appropriate scale, though only some are commercially viable. This paper examines each of those production routes and predicts which will be used to provide an adequate supply of Ac-225 within the next few years.

Ac-225 Production Methods

1. Separation of Th-229 From Existing Finite Amount of Uranium-233 (U-233)

Historically, the primary supply of Ac-225 in the United States has been from the United States Department of Energy (DOE). Ac-225 can be separated from Th-229. Th-229 is a decay product of U-233, from which Th-229 can be chemically extracted.

As shown in **Table 1**, the DOE currently holds nearly

Isotopic Quality	Total U (kg)	Isotopics		Uses	
		^{233}U (kg)	^{232}U (ppm)[c]	Medical ^{299}Th (g)	Other[9]
High	269.0	256.3	<15	23.9	Yes
Intermediate	108.0	95.5	>100	8.7	Yes
Low	1085.2	102.0		12.5	No
Totals	1462.2	453.8		45.1	

Table 1. Quality of Major Batches of Separated U-233 in Inventory at Oak Ridge National Laboratory (ORNL).[10]

[5] Images from Shea, SB, *op. cit.*, but originally published in Kratochwil, *op. cit.*

[6] Boll, RA, Malkemus D, and S Mirzadeh. 2005. *Production of actinium-225 for alpha particle mediated radioimmunotherapy.* APPL RADIAT ISOT 62:667-679. doi:10.1016/j.apradiso.2004.12.003

[7] Harvey, JT. 2018. *NorthStar Perspectives for Actinium-225 Production at Commercial Scale.* CURR RADIOPHARM 11:180-191. doi:10.2174/1874471011666180515123848

[8] Nihon Medi-Physics Co., Ltd. 05APR2022. *News Release: Nihon Medi-Physics Attains World's First Manufacturing of Actinium-225 with Cyclotron on Production Scale for Investigational Drugs.* https://tinyurl.com/bdn5r9sn.

[9] U-233 has multiple uses, including a medical use for a U-233 decay product. The quantity of the decay product depends upon how long the U-233 has been in storage since it was last purified.

[10] Adapted from Forsberg, CW. 22MAR2000. *Quality of Major Batches of Separated 233U in Inventory at Oak Ridge.* Briefing for US Department of Energy, Oak Ridge, TN. https://tinyurl.com/7je4pjhb. For comparison with other weapons-usable materials, the plutonium inventory is ~100 metric tons, and the high-enriched uranium (HEU) inventory is several hundred metric tons. Only ORNL U-235 inventory is shown; the Idaho National Engineering and Environmental Laboratory ("INEEL") also has inventory of high-isotopic-quality U-233 from its Light-Water Breeder Reactor Program. The estimated inventory is 351.4kg, most of which is in the form of UO_2 mixed with 14 tons of ThO_2. The cost to separate U-233 from thorium would be significant, and DOE has disposed of and buried this material at its Nevada test site.

1.5 metric tons of uranium as legacy material from the 1950s and 1960s. This inventory contains 453 kg of U-233. Through the program mentioned above from 1994, a small proportion of this uranium stockpile was processed resulting in a quantity of approximately 150 mCi of Th-229. Unfortunately, this Th-229 can provide only about 1.2 Ci of Ac-225 per annum, enough for approximately 1200 patients.

In 2019, through a public-private partnership between the DOE, Isotek, and TerraPower, the United States government and those private partners are implementing a project to extract Th-229 from the legacy U-233 material before these stocks are disposed of. TerraPower intends to harvest Ac-225 from the recovered Th-229 using advanced radioisotope generator technology. The company is developing these generators to increase efficiency and automation of Ac-225 supply intended for clinical trials and development of advanced therapies for the treatment of cancer.[11]

It is likely that only the high-isotopic-quality material can be used. The intermediate-quality material is contaminated with uranium-232 (U-232), of which thallium-208 (Tl-208) is a decay product, which has a high-energy decay and therefore requires extensive shielding. The low-quality material is in the form of laboratory waste such as vials, reagents, protective equipment, etc, and therefore extraction of Th-229 will be challenging.

It is thought that this production method is capable of producing Ac-225 but potentially less than 20% of the required quantities long-term. It is expected this production route will come online, but at a limited scale, in late 2023.[12] In addition, this method also is limited to existing stockpiles of DOE material as previously discussed.[13]

2. Cyclotron Production via Radium-226 (Ra-226) (p,2n) Ac-225

Cyclotron production of Ac-225 involves irradiating a Ra-226 target with a proton and knocking off 2 neutrons. Drawbacks to this method include handling a radium target, resulting in the need to mitigate radon off-gas.

Another lesser-known drawback is the side reaction that produces actinium-226 (Ac-226), which has a 1.2-day half-life compared to a 10-day half-life for Ac-225. It has been reported that the activity ratio of Ac-226 to Ac-225 is as much as 3% at 4 days post-irradiation.[14] Waiting for the bulk of Ac-226 to decay means significant amounts of Ac-225 will be lost. It is unknown how the FDA will manage the presence of Ac-226 in the Ac-225 and how much Ac-226 will be allowable.[15]

The uncertainty in the regulatory environment means that this method may experience added challenges to become commercially viable.

3. Nuclear Reactor Production of Th-229 via Ra-226 (xn,xαβγ) Th-229 or Th-228 (n,γ) Th-229

Reactor production of Th-229 from Ra-226 is a process that does not produce a high yield and has added complications, including handling the Ra-226 and mitigating radon off-gas from the process.

In reactor production, Th-229 is produced from neutron transmutation of Ra-226. Irradiation of Ra-226 targets at the ORNL High Flux Isotope Reactor resulted in yields of Th-229 at 26 days of 74.0 MBq/g ± 7.4 MBq/g (2 mCi/g ± 0.2 mCi/g).[16] This is a small increase in the overall total stock of Th-229. The test irradiations performed by ORNL used targets of a few 10s of micrograms. That data scaled showed that a 1 g target irradiated for ~25 days could yield about 12 mCi of Th-229. By comparison, the current DOE Ac-225 production of about 1000 mCi annually comes from a Th-229 source. The source is about 10 times larger. In addition, both Th-228 (requiring extensive shielding and ventilation) and Ac-227 (a problematic contaminant) are co-produced using this process.

These issues could imply this route may not be a viable commercial production route.

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[11] 11APR2023. *Press Release: TerraPower, Cardinal Health, Isotek, and DOE Celebrate Historic Achievement in Next Generation Cancer Treatment*. US Department of Energy. https://tinyurl.com/3wn762py.

[12] Id.

[13] Id.

[14] Harvey, JT, op. cit.

[15] Kasliwal, R. *Product Quality Considerations in Actinium-225 Radiopharmaceuticals*. FDA-NRC Workshop: Targeted Alpha Emitting Radiopharmaceuticals, with Focus on Ac-225. 22SEPT2021.Session II. https://tinyurl.com/59tpdxa5.

[16] Hogle, S, Boll, RA, Murphy, K, et al. 2016. *Reactor production of Thorium-229*. APPL RADIAT ISOT 114:19-27. doi:10.1016/j.apradiso.2016.05.002

4. High-Energy Proton Spallation of Thorium-232 (Th-232) (p, xnp) Ac-225 + Others

Another currently known and investigated production route is high-energy proton spallation of a Th-232 target. This process involves irradiating a Th-232 target with high-energy protons via a large cyclotron or linear accelerator, causing destruction of the thorium nucleus and production of Ac-225 and multiple other isotopes. TRIUMF and the DOE Tri-Lab programs are working independently on this process.

This process requires a proton beam energy greater than 70 MeV, and there are few such accelerators in North America capable of achieving at least that beam energy, which may limit commercial viability. Another drawback to this process is the creation of many side reactions, including the creation of Ac-227 in the order of 0.1% of the total actinium activity at end of irradiation, as well as significant amounts of Ac-226. More importantly, by mass, the amount of Ac-225 and Ac-227 are roughly equal, which may create labeling effect challenges. In addition, Ac-227 has a 22-year alpha-emitting half-life, which presents significant waste challenges for the hospitals and clinics where this material will be used. The only useful benefit of spallation is production of a small amount of radium-225 (Ra-225), which could be used to produce Ac-225 without Ac-227 contamination.

5. Electron Accelerator Photonuclear Transmutation of Ra-226 via Ra-226 (γ,n) Radium-225 (Ra-225)→Ac-225

Photonuclear transmutation involves the use of an electron accelerator to irradiate a Ra-226 target with high-energy photons, or bremsstrahlung. This process knocks off a neutron from Ra-226 and creates Ra-225, the parent of Ac-225.

This process also requires handling a radium target and mitigating radon off-gas as noted above. Ac-227 is also present; however, it is at least 2 orders of magnitude lower at the end of irradiation compared to other methods, and low enough that it can be fully removed by purifying the Ra-225. Once purified, the Ra-225 is placed in an Ac-225 generator to obtain Ac-225 free of Ac-227 (known as "non-carrier added" or "n.c.a." Ac-225).

After a sufficient amount of Ac-225 has built up in the generator, it is extracted from the Ra-225 source, purified, and collected. This process is repeated for multiple weeks using the same Ra-225 source, resulting in efficient production of n.c.a. Ac-225. Using Ra-225 sources repeatedly results in an uninterrupted supply of n.c.a. Ac-225 for the multi-week life of the generators.

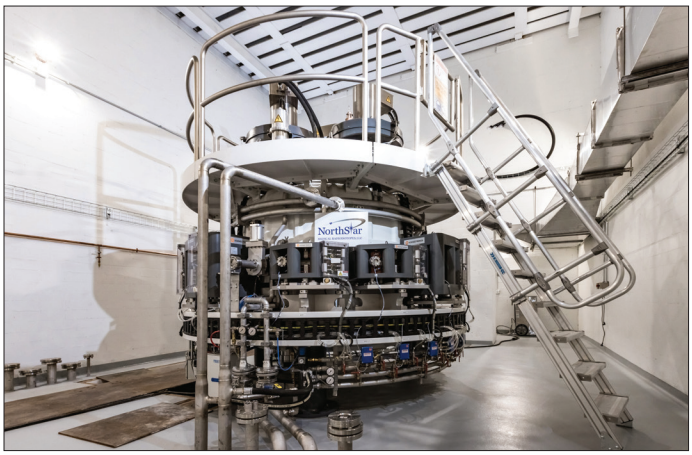

Figure 2. Ion Beam Applications (IBA) Rhodotron® TT300-HE electron accelerator, located in NorthStar's Ac-225 production facility, Beloit, WI.

NorthStar investigated several routes for the production of Ac-225 and concluded that the photonuclear transmutation route is by far the best commercial production method.

NorthStar Medical Radioisotopes and Electron Accelerator Photonuclear Transmutation

In September 2021, NorthStar held a groundbreaking ceremony on a 30,000-sq ft facility dedicated to the production of commercial-scale n.c.a. Ac-225. This process uses a dedicated IBA Rhodotron® TT300-HE electron accelerator (**Figure 2**). NorthStar received this electron accelerator on February 22, 2023. This production route is highly scalable and has the capability to produce up to 200 Ci per year of n.c.a. Ac-225 per electron accelerator. Due to the scalable nature of this process, production can grow with market demand very efficiently.

NorthStar's campus in Beloit, Wisconsin, is located next to a power substation designed to accommodate redundant mechanical systems and power supplies. This allows for high reliability of electrical feed to the site for all NorthStar's production needs.

To ensure success, NorthStar leveraged a network of engineering, building, and design companies who worked to build the first-in-kind molybdenum-99/copper-67 accelerator program. NorthStar will be able to move shipments of n.c.a. Ac-225 through its distribution network,

where product shipments will be monitored and tracked through an established transportation and logistics process from its headquarters in Beloit, WI.

Summary

Each production route for Ac-225 has its own set of unique challenges. Building on years of research, knowledge, and isotope production experience, NorthStar has embarked on a solution to create a domestic source of this powerful alpha-emitting radiopharmaceutical therapy. NorthStar, leveraging prior experience, has chosen the electron accelerator production method as it provides the best option for sustainable, scalable, and reliable production of n.c.a. Ac-225.

Major advances in radiopharmaceutical therapy show significant promise for the treatment of cancer and other serious diseases. For these advances to positively impact patient health care, they will require a significant increase in isotope production that is not dependent on aging nuclear reactors but instead relies on the development of a modern, robust, and commercial-scale supply chain.

The use of electron accelerators provides a path for the commercial-scale production of high-quality isotopes, continuing NorthStar's approach of producing medically significant radioisotopes with minimal radioactive waste. Simply put, the reliable, scalable production of n.c.a. Ac-225 has immense potential to accelerate treatment options for millions of patients with cancer and other serious diseases.