Production and supply of alpha particles emitting radionuclides for Targeted Alpha Therapy (TAT).

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Abstract

Encouraging results of Targeted Alpha Therapy (TAT) have created significant attention from academia and industry. However, the limited availability of suitable radionuclides has hampered widespread translation and application. In the present review, we discuss the most promising candidates for clinical application and the state of the art of their production and supply. Along with forthcoming two reviews on chelation and clinical application of alpha-emitting radionuclides, JNM will provide a comprehensive assessment of the field.
**Introduction**

Targeted Radionuclide Therapy (TRT), has seen important clinical breakthroughs, notably originating from the successful clinical translation of Prostate Specific Membrane Antigen (PSMA) and Somatostatin Receptor targeted therapy with β⁻ emitters (notably $^{177}$Lu) (1,2).

Alpha-emitting radionuclides have also been applied successfully in research and clinic. While not a bioconjugate, the clinical approval of Xofigo® ($^{223}$RaCl₂) represented an important milestone in the translation and application of alpha emitter based radiopharmaceuticals (3).

Improved access to a portfolio of selective alpha(α)-emitting bioconjugates and radiopharmaceuticals is an important requirement for preclinical evaluations, clinical trials, and translation (4,5).

TAT combines α-emitting radionuclides with selective delivery systems (e.g. peptides, antibodies, etc.). Owing to their high Linear Energy Transfer (LET) and high energy (several MeV’s), TAT radiopharmaceuticals deliver therapeutic power within a range of few cell diameters. This generates maximal damage of targeting cells while minimizing off-target effects on healthy tissues (6).

Significant efforts are required to optimize the formulation of stable radiopharmaceuticals, determine microdosimetry, and progression of clinical studies.

However, the major bottleneck for conducting translational research with alpha emitters is their limited availability. High Z of TAT radionuclides resulting in complex production and lengthy irradiations using powerful reactors or cyclotrons creates this problem. Alternatively, irradiations of highly radioactive targets at specialized facilities or generation from uncommon isotopes may be required. Therefore, the demand for alpha emitters often significantly exceeds availability and supply.
Several comprehensive reviews about various aspects of TAT, including radiochemical considerations (7), and preclinical and clinical applications have been published (8,9).

Here we asked a group of experts to highlight research challenges and opportunities for the rapidly evolving field of TAT. We provide the State of the Art in production and supply of the most potent clinically relevant α-emitters. We also highlight discrepancies between demand and availability.

Member States have asked the International Atomic Energy Agency (IAEA) to assist with capacity building and technology transfer for the development, production, and quality control of new generations of therapeutic radiopharmaceuticals, including alpha emitters. During several Technical Meetings at IAEA in 2013 (10), 2018 (11), and 2019, the demand, production routes, radiopharmaceutical aspects, and supply of $^{225}$Ac have been extensively discussed. IAEA will in the future provide guidelines to the Member States for production, quality control, pre-clinical tests, and waste management of alpha-radiopharmaceuticals.

In the following section, we discuss production and supply aspects of candidates that are currently in the clinical practice (namely $^{227}$Th/$^{223}$Ra, $^{225}$Ac, $^{211}$At, and $^{212}$Pb/$^{212}$Bi) and also several promising candidates that are in pre-clinical evaluation ($^{230}$U/$^{226}$Th and $^{149}$Tb).

* All nuclear decay data are taken from NuDat 2.8 library: https://www.nndc.bnl.gov/nudat2/
Clinically relevant alpha emitters

$^{227}$Th (Thorium)/$^{223}$Ra (Radium)

FIGURE 1. Decay scheme of $^{227}$Ac.

Starting from $^{227}$Ac ($t_{1/2}$ 21.77 y), two nuclides for TAT-applications can be extracted: $^{227}$Th ($t_{1/2}$ 18.7 d) and $^{223}$Ra ($t_{1/2}$ 11.43 d) (Figure 1). Despite their chemical differences, they are grouped due to their common starting material, similar to $^{225}$Ac and $^{213}$Bi or $^{224}$Ra and $^{212}$Pb. Thus, before exploring the current use of $^{227}$Th and $^{223}$Ra, the production of $^{227}$Ac needs to be described.

$^{227}$Ac is primarily produced via neutron irradiation of a $^{226}$Ra target in a nuclear reactor ($I2$). Several limitations relevant to $^{226}$Ra ($t_{1/2}$ 1600 y) as a target material need to be considered: the
target is highly radioactive with the $^{222}\text{Rn}$ ($t_{1/2}$ 3.82 d) daughter as a radioactive gas; further, limited quantities of $^{226}\text{Ra}$ are currently available. For an efficient process, a high flux of thermal neutrons is preferable, as $^{226}\text{Ra}$ does have a fission cross-section for neutrons with energy above 1 MeV ($I_3$). Due to the increased focus of medical authorities on production quality, a specification of the target material may be required to ensure the quality of the $^{227}\text{Ac}$ product.

After $^{226}\text{Ra}$ target irradiation, the purification of $^{227}\text{Ac}$ from the target is the next step. This is accomplished by separation using liquid chromatography techniques, similar to the procedure for separation of $^{229}\text{Th}$ from $^{225}\text{Ac}$ and $^{225}\text{Ra}$ ($I_4$). The separation process needs to remove all radium and all thorium, as both $^{228}\text{Th}$ and $^{229}\text{Th}$ will be present as by-products after irradiation along with the remaining $^{226}\text{Ra}$. After $^{227}\text{Ac}$ purification, characterization of the actinium is recommended, to have as much data on the starting material as possible. The $^{227}\text{Ac}$ is typically kept in a dilute nitric solution but may be dried down to actinium nitrate if the material is to be shipped, due to the shipment of dry material that is easier than a shipment of a solution, based on the current IATA regulations ($I_5$).

Alternative approaches include the recovery of $^{227}\text{Ac}$ from legacy Ac-Be neutron sources ($I_6$) and the accelerator-based production of $^{225}\text{Ac}$ using $^{232}\text{Th}$ as a target generating small quantities of $^{227}\text{Ac}$ as a by-product ($I_7$).

It should be noted that there was virtually no production of $^{227}\text{Ac}$ between the 1970s and the past decade. Thus, the availability of $^{227}\text{Th}$ and $^{223}\text{Ra}$ was very limited.

$^{227}\text{Th}$ is harvested from a generator containing $^{227}\text{Ac}$. Using separation columns, it is possible to separate thorium from actinium and radium, thus removing both the mother and the daughter nuclides. The purified thorium may be used on-site for immediate labeling or shipping, as
thorium chloride, to the labeling site. If shipment or labeling is delayed, the purification step for removal of radium may be repeated to minimize dose contribution from daughters. 

$^{223}\text{Ra}$ is harvested also from a generator containing $^{227}\text{Ac}$. Using separation columns, radium can be separated from actinium and thorium, thus removing both mother nuclides. The purified radium is typically used on-site for drug formulation immediately or shipped as dry radium chloride.

Both $^{223}\text{Ra}$ and $^{227}\text{Th}$ are currently commercially available from Oak Ridge National Laboratory (ORNL) through the US Isotope Distribution Office, and Pacific Northwest National Laboratory (PNNL), Rosatom, and Bayer have access to $^{223}\text{Ra}$ and $^{227}\text{Th}$.

Radium was considered a good candidate for TAT, but over the last decades, no suitable chelator has been found. However, $^{223}\text{Ra}$ in its ionic form is clinically used as Xofigo® in the treatment of bone metastatic prostate cancer (18). This does not involve a chelator or a target-seeking moiety. Xofigo® thus represents a special form of a TAT pharmaceutical. The use and handling of Xofigo®, which is currently approved in 53 countries, form the basis for any subsequent TAT pharmaceuticals including the European Union, the United States of America, and Japan.

Because of their short half-lives, all daughters are in radioactive equilibrium with $^{223}\text{Ra}$ at the time of injection. The shelf-life of a radiopharmaceutical will be governed by a number of parameters, including activity of the mother nuclide, ingrowth of radioactive daughters and degradation of the pharmaceutical due to radiolysis of one or several components. In the case of Xofigo, the ingrowth of daughters is not a limiting factor, as the daughters are fully ingrown after some hours. Radiolysis of the pharmaceutical is a concern, in particular the radiolysis of the citrate buffer. In addition, the lower specific radioactivity after several half-lives is also a concern. In order to determine a proper shelf-life, these aspects must be taken into account and
studies must be conducted. In the case of Xofigo, a shelf-life of 28 days was therefore adapted. It should be emphasised that this is unusually long for a radiopharmaceutical, partly due to the half-life of $^{223}$Ra and partly due to the low impact of radiolysis. This allows for global distribution independent of production site location. For research applications, the availability of $^{227}$Ac, $^{227}$Th and $^{223}$Ra is currently sufficient, but the overall supply for clinical or commercial use is less certain. No published data on the production capacity for the different suppliers are available.
225Ac (Actinium)\(^{213}\)Bi (Bismuth)

**FIGURE 2. Decay scheme of \(^{233}\)U.**

Actinium-225 is one of the most promising TAT radionuclides with a half-life of 9.92 days and a net emission of 4 \(\alpha\) particles in the decay chain. It can be used for TAT radiopharmaceuticals or as a source of \(^{213}\)Bi (\(t_{1/2} \) 45.61 min) which also can be applied in TAT (19).

There are several production routes for \(^{225}\)Ac (20). The two most important ones are: i) separation from the natural decay of \(^{229}\)Th obtained from waste stockpiles containing \(^{233}\)U; ii) the irradiation of \(^{232}\)Th with high-energy protons (>70 MeV) via the fission reaction \(^{232}\)Th(p,x)\(^{225}\)Ac.
In addition, irradiation of $^{226}$Ra with lower-energy protons (<25 MeV) via the reaction $^{226}$Ra(p,2n)$^{225}$Ac holds great promise for large quantities due to high (710 mb) cross-section peak at 16.8 MeV(21). This reaction could be performed on many of the low-energy cyclotrons already in use for medical isotope production. However, irradiating a highly radioactive target on these medical cyclotrons and limited radium quantities have rendered this approach used infrequently. Another promising route is photonuclear production via $^{226}$Ra($\gamma$, n)$^{225}$Ra→$^{225}$Ac which can provide the clinically relevant supply of $^{225}$Ac (22).

**Production of $^{225}$Ac from $^{229}$Th decay**

$^{225}$Ac is most frequently produced from $^{229}$Th generators. $^{229}$Th is the grand-parent isotope of $^{225}$Ac in the decay series of $^{233}$U (Figure 2) and has a half-life of 7932 years (NuDat), later corrected to 7917 years (23). As such, $^{229}$Th serves as an ideal radioisotope generator for a virtually perpetual supply of $^{225}$Ac. The primordial neptunium decay chain to which $^{229}$Th belongs is now extinct; therefore, the availability of $^{229}$Th that is suitable for use via separation technology is limited. The most common source of $^{229}$Th is the decay of anthropogenic $^{233}$U. Due to safeguarding and non-proliferation efforts surrounding $^{233}$U, access to large quantities is limited and only approximately 12.9 GBq (350 mCi) of $^{229}$Th has been converted into functioning $^{225}$Ac generators to date; this has limited the global annual production of $^{225}$Ac to approximately 63 GBq (1.7 Ci) (20).

By allowing the $^{225}$Ra ($t_{1/2}$ 14.9 d) and $^{225}$Ac ($t_{1/2}$ 9.92 d) progeny of $^{229}$Th to approach secular equilibrium (Figure S1, Supplemental material) over typically 30-90 days, the generator can be eluted to separate the shorter-lived daughters. Following the initial milking of the $^{229}$Th generator, $^{225}$Ra can be stored for further use as a parent-daughter generator of a reduced but still
relevant quantity of $^{225}$Ac. The frequency of $^{229}$Th and $^{225}$Ra generator elution is often determined with considerations for both batch size requirements, operational cost, and generator size. Generators with larger amounts of $^{229}$Th can produce suitable $^{225}$Ac batch sizes with higher frequency. Following elution, selective isolation and careful quality control are performed to prepare $^{225}$Ac suitable for incorporation into radiopharmaceuticals.

There are multiple $^{229}$Th generators in operation, capable of producing $^{225}$Ac in quantities relevant for preclinical and limited clinical use. The Directorate for Nuclear Safety and Security of the Joint Research Centre in Karlsruhe, Germany (Figure S2, Supplemental material) possesses $\sim$215 mg of $^{229}$Th (24), while the Leypunsky Institute for Physics and Power Engineer (IPPE) in the Russian Federation (Figure S3, Supplemental material) (25) and ORNL in the USA (26) each possess 700 mg of $^{229}$Th. The additional source became recently available at Canadian Nuclear Laboratories (CNL) in Canada (Figure S4, Supplemental material) (27) with 50 mg of $^{229}$Th.

All generators rely on an anion exchange mechanism for the separation of $^{229}$Th from $^{225}$Ra and $^{225}$Ac. Cation exchange or extraction chromatography is used for $^{225}$Ac separation from $^{225}$Ra, while additional anion exchange processing provides purification from residual Th (28). These methods produce $^{225}$Ac with suitable attributes for pre-clinical and clinical applications (7). Molar-specific activity and stable metals content can differ for various $^{225}$Ac sources. $^{233}$U stockpiles are currently being processed at ORNL through a public-private partnership which is expected to yield $\sim$45,000 mg of $^{229}$Th (Table S1, Supplemental material) (29).

This material also contains $^{228}$Th in sufficient quantities (30) to require exposure shielding due to the presence of $^{208}$Tl, complicating generator development and deployment. The work on the
generator for this material is ongoing and it will leverage the techniques and methods employed in the existing generators (31).

**Production of $^{225}$Ac via proton-irradiation of $^{232}$Th**

$^{225}$Ac has been produced by spallation reaction $^{232}$Th(p,x)$^{225}$Ac on thorium targets with proton energies ranging from 100 to 1400 MeV at beam currents as high as 250 $\mu$A. This method of production is presently under development as part of the US Department of Energy’s (US DOE) Tri-Lab Effort, involving Brookhaven National Laboratory (BNL) and Los Alamos National Laboratory (LANL) for target irradiations and Oak Ridge National Laboratory (ORNL) for subsequent radiochemical processing and dispensing of irradiated targets. The current focus of the US DOE Tri-Lab Effort is to bring co-located processing facilities on-line at BNL and LANL in the 6 months to 5 years timeframe with the goal of greater than monthly production of Ci-scale batches. The US DOE Tri-Lab effort has established processing under cGMP conditions with operations captured under a Drug Master File (32,33).

In addition, efforts are underway to develop spallation production capabilities in Canada utilizing a diverse set of irradiation capabilities at TRIUMF (up to 500 MeV proton beams). Producing $^{225}$Ac at higher proton energy results in a higher fraction of $^{225}$Ac vs $^{227}$Ac (*Figure S5, Supplemental material*). This is currently being pursued with TRIUMF’s 500 MeV cyclotron. About 200 MBq (5.4 mCi) quantities of $^{225}$Ac are produced with a proton beam of ~480 MeV on target. In addition, significant amounts of $^{225}$Ra are also produced, which can be separated and used as a generator isotope for isotopically pure $^{225}$Ac (*Figure S5, Supplemental material*). In recent 25 mA-hr irradiations of ~8 g targets of $^{232}$Th, isolation of the radium fraction provided sufficient $^{225}$Ra to yield ~18 MBq (~0.5 mCi) of $^{225}$Ac, with no detectable $^{227}$Ac (see *Figure S6,*
Supplemental material) for the separation and (Figure S7, Supplemental material) for an example of a gamma spectrum (34,35).

Furthermore, work is underway at the Institute of Nuclear Research (INR), Russia and NorthStar Medical Technologies (Beloit, WI, USA) where teams are pursuing spallation production target development and new process technologies (36–38).

In thorium spallation, $^{227}$Ac ($t_{1/2} = 21.77$ y) is co-produced with similar yields as $^{225}$Ac, leading to concerns for facility licensing and the path forward for associated waste streams. Overall $^{227}$Ac activity represents approximately 1-2% of the overall sample activity and has not been demonstrated to impact labeling efficiency with DOTA the gold standard radiolabeling or result in toxicity concerns (39). The concern related to $^{227}$Ac content can be avoided when producing $^{213}$Bi from a generator, which retains all actinium isotopes. This issue can also be addressed by isolating of Ra isotopes and further extracting isotopically pure actinium-225 (40). Additionally, researchers at TRIUMF have demonstrated on-line generation of isotopically pure beams of $^{225}$Ac using a resonant laser ionization method (41), and CERN the separation of pure beams from different thick targets of either $^{225}$RaF$^+$ or $^{225}$Ac$^+$, including molecular ion formation or resonant laser ionization (11). The supply of $^{225}$Ra or $^{225}$Ac from CERN-MEDICIS or ITU, Karlsruhe, will become available for researchers, through a newly approved coordinated European hub, PRISMAP-The European medical isotope program kicked-off in 2021 (42).

Currently, the vast majority of $^{225}$Ac is used in the form of $^{225}$Ac-labeled radiopharmaceuticals (43), both for preclinical developments as well as for clinical studies mainly focusing on the treatment of prostate cancer, neuroendocrine tumors, and gliomas. Although the application of $^{213}$Bi, generated from $^{225}$Ac/$^{213}$Bi generators, has also demonstrated significant clinical benefit
(44), the limited availability and high cost of high activity generators are presently hampering further studies.
At (Astatine)

**FIGURE 3.** Decay scheme of $^{211}\text{At}$.

$^{211}\text{At}$ (Figure 3) is perhaps the easiest $\alpha$-emitting radionuclide to produce. However, its availability has been limited due to the fact that there are few accelerators in the world that produce an $\alpha$-beam with the optimal energy range (28-29 MeV) and beam current (10 mA or higher) to produce adequate quantities for research and clinical applications (5,45,46). Additionally, the relatively short half-life of $^{211}\text{At}$ ($t_{1/2} = 7.21$ h) causes distribution problems. Here the supply model is a network as for instance established by the DOE isotope program.

**FIGURE 4.** Direct and indirect accelerator production routes of $^{211}\text{At}$. $^{211}\text{Rn}$ can also be produced by spallation of actinide targets (uranium or thorium) induced by high-energy protons. (reaction not shown).
The most common method of production uses the $^{209}\text{Bi}(\alpha,2n)^{211}\text{At}$ reaction where a metallic bismuth target is bombarded with $\alpha$-particles (Figure 4). Inexpensive naturally abundance monoisotopic bismuth (available at 99.999%), can be used directly for target preparation. In general, the bismuth metal is melted onto or is deposited from a vapor onto aluminum or copper backing. Bismuth metal, while inexpensive, is a poor thermal conductor and has a low melting point ($272^\circ\text{C}$). Thus, effective cooling methods to prevent the target from melting during irradiations are required (47). Thick targets (80 µm) are desired for production and to keep the beam from hitting the target backing, but thinner targets allow the most efficient cooling. Alternate bismuth target materials with higher melting points, such as Bi$_2$O$_3$, can be used in irradiations, but thus far none have proven to be superior to bismuth metal in the production of $^{211}\text{At}$.

The incident energy of the $\alpha$-beam in bismuth irradiations is very important for optimizing $^{211}\text{At}$ production rates and to minimize the production of an unwanted radionuclide, $^{210}\text{At}$. Production of $^{210}\text{At}$ ($t_{1/2} = 8.1$ h) is problematic as it decays to a long half-life $\alpha$-emitter $^{210}\text{Po}$ ($t_{1/2} = 138.38$ d). Although $^{210}\text{Po}$ is found in nature, it has high human toxicity. Generally, an energy of 28 MeV $\alpha$-beam has been used to preclude $^{210}\text{At}$ production. In an optimization study at 29 MeV no quantities of $^{210}\text{At}$ were detected (48). At 29 MeV the production rate of $^{211}\text{At}$ was increased by $\sim15\%$ over that of a 28 MeV irradiation. The significant growth in production of $^{211}\text{At}$ can be obtained by increasing the accelerator beam current. Unfortunately, the feasible beam current is inherent to the design of the accelerator. However, a higher beam current can be obtained by irradiating an internal target as beam current is lost during extraction to external beamlines (49).

Isolation of pure $^{211}\text{At}$ from irradiated bismuth targets is also relatively simple compared with other $\alpha$-emitters, as there are no other radionuclides produced under optimal irradiation
conditions. The most common and perhaps simplest method for isolation of $^{211}$At is high temperature (650-700°C) dry distillation. However, there can be radiation safety concerns with volatilized $^{211}$At. Therefore, alternative “wet chemistry” isolation methods are being developed (50,51). To simplify the isolation of $^{211}$At, methods for the automation of dry distillation and wet chemistry approaches are being developed (52).

Current quantities of $^{211}$At are inadequate for widespread clinical use. In fact, only Duke University, and the University of Washington in the United States, and Copenhagen University Hospital in Denmark have produced $^{211}$At for clinical trials.

The Department of Energy Office of Isotope R&D and Production (DOE IP) provides funding to improve the availability of $^{211}$At in the United States. It is also creating a “University Network” for $^{211}$At production in different regions of the US for shipment to users through the DOE National Isotope Development Center. Japan has 5 sites producing $^{211}$At by $\alpha$-beam irradiation for use at 13 user sites. In support of research, the European Union has recently initiated a “COST ACTION (CA19114)” that involves networking of $^{211}$At production centers among a number of European countries.

While the current production of $^{211}$At is limited, accelerators with medium energy $\alpha$-beam can be added at a significantly lower cost than high energy accelerators or nuclear reactors required for the production of other $\alpha$-emitters. Accelerator technology innovations could provide much higher $\alpha$-beam currents than current systems. Although new target technology will be required with higher $\alpha$-beam currents to circumvent target melting, ultimately much larger quantities of $^{211}$At could be produced.

An alternative, early-stage research approach for $^{211}$At production involves irradiation of bismuth metal with lithium ions to produce $^{211}$Rn (Figure 4) for a $^{211}$Rn/$^{211}$At generator. Since $^{211}$Rn has a
half-life of 14.6 h, its decay during transit might provide a more effective distribution of
\(^{211}\text{At}\). Radon is classified as a gaseous element and may not be suitable for chemical operations. However, since it has a high affinity for non-polar organic solvents, it is possible to make a generator by applying the solvent extraction method (53). Such a generator system has been demonstrated where gaseous \(^{211}\text{Rn}\) was isolated and retained in liquid alkane hydrocarbon (dodecane) and \(^{211}\text{At}\) generated from the \(^{211}\text{Rn}\) source was extracted in an aqueous solution (2 N NaOH) (54).
Both $^{212}\text{Bi}$ ($t_{1/2} = 60.55\text{ min}$) and $^{212}\text{Pb}$ ($t_{1/2} = 10.64\text{ h}$) are part of the $^{232}\text{Th}$ ($t_{1/2} = 1.4\times10^{10}\text{ y}$) and $^{232}\text{U}$ ($t_{1/2} = 68.9\text{ y}$) decay chain, with $^{212}\text{Bi}$ being the decay daughter of the $^{212}\text{Pb}$ (Figure 5). $^{212}\text{Pb}$ emits two $\beta^-$ and one $\alpha$ particle through its decay to stable $^{208}\text{Pb}$, while $^{212}\text{Bi}$ emits one $\beta^-$ and one $\alpha$ particle which can be used for TRT. Either radionuclide is commonly isolated from $^{228}\text{Th}$ sources (vide infra), which is a decay daughter of both $^{232}\text{Th}$ and $^{232}\text{U}$.

A major drawback in using $^{212}\text{Bi}$ clinically is the emission of a relatively intense and very high energy gamma-ray (2.6 MeV of 36% intensity per decay of $^{212}\text{Bi}$) via its daughter thallium-208.
This also creates an obstacle for handling $^{228}\text{Th}$ sources, leading to stability issues due to radiolytic damage of generator systems, and mandates significant shielding for operators. These issues have been noted for newly available $^{229}\text{Th}$ that contains $^{228}\text{Th}$ in relatively high quantities (see $^{225}\text{Ac}/^{213}\text{Bi}$ section).

Using $^{212}\text{Pb}$ as an *in vivo* generator, instead of $^{212}\text{Bi}$ directly, in radiopharmaceutical development, reduces the amount needed for therapy 10-fold. It also facilitates radiopharmaceutical production, formulation, and administration given its longer half-life. However, the issue of daughter recoil following beta decay and subsequent retention of progeny needs to be taken into consideration, similar to other alpha emitters discussed.

$^{212}\text{Pb}$, and thus $^{212}\text{Bi}$ are isolated from $^{228}\text{Th}$ or $^{224}\text{Ra}$ generators, both of which are natural decay products of $^{232}\text{Th}$. $^{228}\text{Th}$ can be obtained through the isolation of $^{228}\text{Ra}$ in annual intervals from $^{232}\text{Th}$ or by isolating from anthropologic sources via $^{232}\text{U}$ stockpiles (a portion of which have been transferred by the Department of Defense to AlphaMed, Inc. from stocks at ORNL, or by the double neutron capture and successive $\beta^-$ decay of $^{226}\text{Ra}$).

Isolation from natural $^{228}\text{Ra}$ remains difficult given the need to process tons of aged $^{232}\text{Th}$ to obtain useable amounts. Each ton of >35-year-old $^{232}\text{Th}$ can yield approximately 3.7 GBq (100 mCi) of $^{228}\text{Ra}$. The French biotech company OranoMed, extracts $^{212}\text{Pb}$ from natural thorium salt. Subsequent separation, purification, and concentration of elements decaying from $^{232}\text{Th}$ provide worldwide shipment of $^{212}\text{Pb}$ generators.

$^{228}\text{Th}$ can be produced from successive neutron capture and $\beta^-$ decay of $^{226}\text{Ra}$. In the past, this production was proven to be feasible, but further process development is needed to determine production yields and cost.
Around 555 MBq (15 mCi) $^{224}$Ra/$^{212}$Pb/$^{212}$Bi generators are available through the US DOE Isotope Program (via ORNL) (58). The current generator is only sufficient for preclinical development (not clinical use), as radiolytic damage limits the scale-up (59). Briefly, $^{224}$Ra ($t_{1/2} = 3.63$ d) is separated from immobilized $^{228}$Th adsorbed onto an organic cation exchange resin (highly cross-linked MP-50, ~300 µL in volume). A $^{212}$Pb and $^{212}$Bi mixture is eluted with a few mL of 2 M HCl or 0.5 M HI with ~70% yield and parent breakthrough of $10^{-6}$. It is also possible to elute $^{212}$Bi (free from $^{212}$Pb) selectively with 0.5 M HCl or 0.15 M HI. The $^{224}$Ra/$^{212}$Pb/$^{212}$Bi generator has a shelf-life of about 2 weeks.

Westrøm et al. (60) prepared a $^{228}$Th/$^{224}$Ra generator based on thorium purchased from Eckert & Ziegler. In this process $^{228}$Th was immobilized on a DIPEX® (Eichrom, Lisle, IL, USA) actinide resin, by mixing $^{228}$Th in 0.1 M HNO$_3$ with a portion of the actinide resin and after a few hours loaded onto a column containing a small portion of inactive actinide resin to avoid breakthrough. $^{224}$Ra could be eluted regularly from the generator column with 1 M HCl.

McNeil et al. (61) reported the preparation of a novel $^{228}$Th/$^{212}$Pb generator by utilizing $^{228}$Th produced as a by-product of $^{232}$Th spallation with 500 MeV protons at TRIUMF. The bulk Th (8 g) (co-precipitated with $^{228}$Th) was purified via anion exchange resin. $^{228}$Th did not absorb to the column and was found in load and wash fractions, which were collected, evaporated to dryness and re-dissolving in 1 M HNO$_3$ to produce the generator stock solution. The separation of $^{212}$Pb from $^{228}$Th was accomplished by passing the generator stock solution through an 80 mg PB resin.

**Research candidates**

There are several hundreds of alpha emitters in the chart of radionuclides, however, most of them are not suitable for TAT due to their half-life, and/or difficulties with the production and
formulation of radiopharmaceuticals. However, with emerging alternative production routes and advancement in chelation systems several additional candidates are of interest for TAT.
$^{230}\text{U (Uranium)/}^{226}\text{Th (Thorium)}$

**FIGURE 6. Decay scheme of $^{230}\text{Pa}$.

$^{230}\text{Pa}$ can be used for TAT directly or as a generator source of shorter-lived $^{226}\text{Th}$ ($t_{1/2} = 30.57$ min). One potential advantage over $^{225}\text{Ac}/^{213}\text{Bi}$ is that $^{230}\text{U}/^{226}\text{Th}$ has multiple alpha decays with very short-lived daughters (seconds) which potentially may prevent significant delocalization of daughters after the decay from the targeting site (Figure 6). One of the main challenges using $^{230}\text{U}$ in similar fashion as $^{225}\text{Ac}$ for direct labeling of biomolecules (e.g. antibodies or peptides) is still relatively undeveloped chelation of uranium for
radiopharmaceutical application and for $^{230}$U/$^{226}$Th generator shorter half-life of $^{226}$Th may represent challenges in term of logistic and radiopharmaceutical synthesis when used in the same way as $^{213}$Bi. $^{230}$U can be produced either directly by proton or deuteron irradiation of $^{231}$Pa ($t_{1/2}$ 3.276x10⁴ y) (62,63) or by decay of $^{230}$Pa ($t_{1/2}$ 17.4 d) which can be produced by spallation of $^{232}$Th (64–66). For the first route production rate is 0.25 MBq (6.7 µCi)/µAh for 25 MeV energy (65) and limiting factors are the handling and availability of the target material. For the second route, the main limitation is that only 7.8% of produced $^{230}$Pa decays to $^{230}$U which significantly decreases the final yield. $^{230}$Pa can also be produced as a by-product during proton spallation of $^{232}$Th and co-extracted along with other medical radionuclides (67) e.g. $^{225}$Ac. Radiochemical processing is required for the Pa, U, and Th which is already well-known and can be achieved by a combination of ion exchange and solid-phase extraction chromatography. Based on similar required clinical quantities of $^{225}$Ac, $^{230}$U can be produced (GBq’s (tens of mCi)) via both routes; however, currently low demand and absent of suitable chelation system for uranium limit application of this attractive radionuclide.
149Tb (Terbium)

FIGURE 7. Decay scheme of 149Tb.

149Tb (t½ 4.118 h) is the lightest alpha-emitters if one excludes the extremely short (108Te) or long half-life (146Sm). It was recognized long ago as an alpha-emitting radionuclide with potentially interesting properties (Figure 7), as it demonstrated single cancer cell-killing capabilities in vitro and is part of a Terbium theranostic quadruplet covering the different nuclear medicine modalities in therapy and diagnostics (68–70). Cyclotron irradiation of Gd targets with high energy protons (70-200 MeV) and spallation reactions of protons at high energy (>1GeV) on thick tantalum targets are the most favorable production routes. In all cases, mass separation is required to suppress co-produced Terbium radionuclides, with demonstrated efficiencies of 12% at CERN-MEDICIS, and of 50% with stable Terbium tracers at LARISSA isotope separator at the University of Mainz (Germany), and for 149Dy production route followed at ISOLDE. Daily cycles of 500 MBq batches are expected from 2021 onwards at CERN-MEDICIS to produce no-carrier added 149Tb radionuclide batches.

The relatively short half-life of 149Tb implies distribution networks mimicking those of many diagnostic radiopharmaceuticals. To support 149Tb distribution, transportation limits have been updated accordingly in 2018 and are no more a limiting factor for the dispatch of relevant activities for clinical applications (71).
While these different alpha emitters have been made available to researchers under different access modalities, a new consortium has been established for funding by the European Commission’s H2020 program. \textit{PRISMAP} comprises important nuclear reactors, accelerators, and isotope mass separation centers. It aims at providing different radionuclides for medical researchers through a single hub, for instance through a single web platform (42). Call for projects, selection by a user access panel, and determination of important nuclear data for proper standardization are fully included in the project’s implementation, with a projected starting date later 2021.

\textit{Discussion}

The current supply of most of the TAT radionuclides is insufficient for pre-clinical and clinical evaluation. Only very few research groups have reliable access to TAT radionuclides due to either high costs or long wait times. Therefore, the supply of $\alpha$ emitting radionuclides for TAT is a pressing issue that needs to be addressed urgently. The current review intends to stimulate discussion and provide useful information on the selection and handling of TAT radionuclides for scientists and clinicians who would like to develop TAT programs. Table 1 summarizes the nuclear properties as well current availability on the clinical scale and potential for future increase in production.

\textbf{TABLE 1.} \textit{Nuclear properties of discussed TAT radionuclides, their current production route/s, and the availability}
Several strategies can potentially solve the supply shortage of TAT radionuclides: (a) to develop alternative production strategies by exploiting existing infrastructure or developing novel approaches; (b) to improving targetry and radiochemical separation strategies enabling to scale up production of TAT radionuclides; (c) to reach a field-wide consensus on the appropriate radionuclidic and radiochemical purity for pre-clinical and clinical applications; (d) to develop a broad portfolio of different chelation and delivery systems to mitigate the physical and chemical limitations of alpha emitters; (e) to define dosimetry and quality standards for clinical applications.

**Conclusions**

The supply and production of alpha emitters are of critical importance when selecting the most suitable candidates for preclinical and in particular clinical TAT. The availability of alpha emitters has slowed down the successful development of radiopharmaceuticals for TAT. Nevertheless, several landmark developments, including the success of Xofigo and $^{225}$Ac-labeled PSMA ligands, demonstrated the great potential of TAT. The strong academic and industry interest further stimulated by these success stories is expected to result in a significantly improved radiopharmaceutical supply in the near future.

**Acknowledgments**

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of astatine-211 at the University of Washington are supported by the U.S. Department of Energy Isotope Program, managed by the Office of Science for Isotope R&D and Production.
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Graphical Abstract

TAT Radionuclides

$^{227}\text{Th}/^{223}\text{Ra}$
$^{225}\text{Ac}/^{213}\text{Bi}$
$^{211}\text{At}$
$^{212}\text{Pb}/^{212}\text{Bi}$
$^{230}\text{U}/^{226}\text{Th}$
$^{149}\text{Tb}$
TABLE 1. Nuclear properties of discussed TAT radionuclides, their current production route/s, and the availability.

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-life</th>
<th>Current Production routes</th>
<th>Availability at clinical scale</th>
<th>Potential to increase production</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{227}\text{Th}/^{223}\text{Ra}$</td>
<td>18.70 d/11.43 d</td>
<td>Decay of $^{227}\text{Ac}$ (generator $^{227}\text{Ac}/^{227}\text{Th}/^{223}\text{Ra}$)</td>
<td>-</td>
<td>Production of $^{227}\text{Ac}$ via neutron irradiation of $^{226}\text{Ra}$</td>
</tr>
<tr>
<td>$^{225}\text{Ac}/^{213}\text{Bi}$</td>
<td>9.92 d/45.61 min</td>
<td>Decay of $^{229}\text{Th}$ (generator $^{229}\text{Th}/^{225}\text{Ra}/^{225}\text{Ac}$) $^{232}\text{Th}(p,x)^{225}\text{Ac}$ ($^{227}\text{Ac}$ contamination or $^{225}\text{Ra}/^{225}\text{Ac}$ generator)</td>
<td>---</td>
<td>Additional stock of $^{229}\text{Th}$ Scaling up spallation on $^{232}\text{Th}$ production $^{226}\text{Ra}(p,2n)^{225}\text{Ac}$ $^{226}\text{Ra}(\gamma,n)^{225}\text{Ra} \rightarrow^{225}\text{Ac}$</td>
</tr>
<tr>
<td>$^{211}\text{At}$</td>
<td>7.21 h</td>
<td>$^{209}\text{Bi}(\alpha,2n)^{211}\text{At}$</td>
<td>--</td>
<td>Explore production at existing and upcoming facilities with alpha beam $^{211}\text{Rn}/^{211}\text{At}$ generator route</td>
</tr>
<tr>
<td>$^{212}\text{Pb}/^{212}\text{Bi}$</td>
<td>10.64 h/60.55 min</td>
<td>Decay of $^{228}\text{Th}$ (generator $^{228}\text{Th}/^{224}\text{Ra}/^{212}\text{Pb}/^{212}\text{Bi}$)</td>
<td>--</td>
<td>Increase production of $^{228}\text{Th}$ (e.g. by-product of $^{227}\text{Ac}$ production and $^{232}\text{Th}$ spallation)</td>
</tr>
<tr>
<td>$^{230}\text{U}/^{226}\text{Th}$</td>
<td>20.8 d/30.57 min</td>
<td>$^{232}\text{Th}(p,3n)^{230}\text{Pa} \rightarrow^{230}\text{U}/^{226}\text{Th}$ $^{231}\text{Pa}(p,2n)^{230}\text{U}/^{226}\text{Th}$ $^{232}\text{Th}(p,xn)^{230}\text{Pa} \rightarrow^{230}\text{U}/^{226}\text{Th}$</td>
<td>---</td>
<td>Developing scale up production for p,3n route Extraction as by-product of $^{232}\text{Th}$ spallation</td>
</tr>
<tr>
<td>$^{149}\text{Tb}$</td>
<td>4.12 h</td>
<td>nat$^{149}\text{Ta}(p,x)^{149}\text{Tb}$ (mass separation)</td>
<td>---</td>
<td>Regular production at CERN_Medicis with PRISMAP initiative Engage other ISOL facilities</td>
</tr>
</tbody>
</table>

"+" – sufficient; "-" – insufficient
Supplemental Materials

FIGURE S1. In-growth of $^{225}$Ra and $^{225}$Ac from $^{229}$Th generator, with milking performed at 60 days (left), and in-growth of $^{225}$Ac from $^{225}$Ra generator (right).

FIGURE S2. Process schematic for isolation of $^{225}$Ac from $^{229}$Th decay as performed at ITU.
FIGURE S3. Process schematic for isolation of $^{225}$Ac from $^{229}$Th decay as performed at IPPE (top). Alpha-spectrum of $^{225}$Ac end product (no peaks of $^{216}$Po and $^{212}$Po) (bottom).
FIGURE S4. Process schematic for isolation of $^{225}$Ac from $^{229}$Th decay as performed at CNL.

FIGURE S5. Cross sections for $^{225}$Ac and $^{225}$Ra production via proton irradiation of $^{232}$Th.
FIGURE S6. Separation scheme of $^{225}\text{Ra}$ from irradiated $^{232}\text{Th}$ target and subsequent $^{225}\text{Ra}/^{225}\text{Ac}$ generator at TRIUMF.
FIGURE S7. Gamma spectrum of purified $^{225}\text{Ac}$ at TRIUMF.

TABLE S1. Thorium Relative Mass Isotopics and Alpha Dose for Current and New Material at ORNL.

<table>
<thead>
<tr>
<th>Th source</th>
<th>$^{228}\text{Th}$</th>
<th>$^{229}\text{Th}$</th>
<th>$^{230}\text{Th}$</th>
<th>$^{231}\text{Th}$</th>
<th>$^{232}\text{Th}$</th>
<th>eV/s for 1 mg from alpha decay</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Material</td>
<td>0.0399</td>
<td>59.5</td>
<td>0.454</td>
<td>1.21E-12</td>
<td>40.0</td>
<td>8.92E13</td>
</tr>
<tr>
<td>Current Generator Material</td>
<td>0</td>
<td>0.66</td>
<td>0</td>
<td>0</td>
<td>99.34</td>
<td>2.49E11</td>
</tr>
</tbody>
</table>