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Astatine-211: Production and Availability

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Abstract

The 7.2-h half life radiohalogen ^{211}At offers many potential advantages for targeted α -particle therapy; however, its use for this purpose is constrained by its limited availability. Astatine-211 can be produced in reasonable yield from natural bismuth targets via the $^{209}\text{Bi}(\alpha, 2n)^{211}\text{At}$ nuclear reaction utilizing straightforward methods. There is some debate as to the best incident α -particle energy for maximizing ^{211}At production while minimizing production of ^{210}At , which is problematic because of its 138.4-day half life α -particle emitting daughter, ^{210}Po . The intrinsic cost for producing ^{211}At is reasonably modest and comparable to that of commercially available ^{123}I . The major impediment to ^{211}At availability is attributed to the need for a medium energy α -particle beam for its production. On the other hand, there are about 30 cyclotrons in the world that have the beam characteristics required for ^{211}At production.

Keywords

Astatine-211; cyclotron; radionuclide; α -particle; targeted radiotherapy

INTRODUCTION

Particularly in clinical settings where tumor burden is low and/or malignant cell populations are located in close proximity to essential normal tissue structures, α -particle emitting radionuclides can offer significant advantages for targeted radiotherapy. Although approximately 100 α -particle emitting radionuclides are known to exist, the number that has been evaluated for this purpose is about an order of magnitude lower. Constraining factors include those related to physical decay characteristics (half life, α -particle emission probability, energy and abundance of other emissions, presence of long lived daughters) as well as other properties including labeling chemistry and toxicity. An additional consideration is the availability of the radionuclide, either as a natural product or from an artificial production source. It is interesting to note that the majority of α -particle emitting radionuclides that have been investigated extensively for use in targeted radiotherapy – ^{212}Bi , ^{213}Bi , ^{223}Ra , ^{225}Ac , ^{227}Th – are products of natural decay chains [1]. The notable exception is the 7.2-h half life radiohalogen ^{211}At , which requires a cyclotron for its production.

Before discussing the details of ^{211}At production and issues related to its limited availability, it is important to review the properties of ^{211}At that contribute to the perspective among many researchers and clinicians that ^{211}At would be the most important α -particle emitting radionuclide if it were widely available. The reader is referred to two reviews discussing the radiochemistry of ^{211}At and its use in targeted radiotherapy [2, 3] for a comprehensive

discussion of these topics. Briefly, the 7.2-h half life of ^{211}At is long enough to permit multi-step synthetic procedures and it is compatible with the pharmacokinetics of a wide variety of potential cell-specific targeting agents. The chemistry of astatine is diverse and while it is possible to exploit its metallic characteristics [4, 5], most strategies for the synthesis of ^{211}At -labeled molecules exploit its halogen properties. Currently, the most widely utilized and versatile approach is the electrophilic astatodemetalation of various organometallic derivatives, especially of organostannanes [6, 7]; however, the formation of astatine-boron bonds via carborane precursors is also useful [8]. As a consequence of its versatile chemistry and intermediate half life (relative to other α -particle emitters), a wide variety of ^{211}At -labeled species have been synthesized and evaluated as targeted radiotherapeutics including colloids, DNA precursors, organic molecules such as *meta*- ^{211}At astatobenzylguanidine, peptides, antibodies and antibody fragments [3]. Considering antibody-based approaches alone, at least 16 different ^{211}At -labeled molecules have been studied [9], reflecting the high level of interest in this α -particle emitter for targeted radiotherapy.

In addition to its half life, ^{211}At possesses other decay properties that are favorable for targeted α -particle radio-therapy. As shown in Fig. (1), the emission of an α -particle is associated with 100% of ^{211}At decays, either directly by α -decay to ^{207}Bi (42%), followed by electron capture decay to stable ^{207}Pb , or by electron capture decay to ^{211}Po (58%) followed by α -emission to stable ^{207}Pb . A potential problem associated with this second decay branch is escape of radio-activity from the site of ^{211}At uptake and decay. However, the problem is much less severe than that associated with the much longer half life α -particle emitting radioactive daughters of ^{225}Ac because the half life of the ^{211}Po intermediate is only 520 msec, limiting its diffusion distance prior to emission of its α -particle. In addition, the potential destabilizing effect of α -particle recoil nuclei on chemical integrity is not a factor because the ^{211}Po is not a daughter created by α -decay. The second decay branch, involving electron capture decay, actually provides an important advantage for ^{211}At - the emission of 77-92 keV polonium K X-rays. These emissions provide a valuable means for tracking ^{211}At in laboratory studies, and for imaging and quantifying ^{211}At activity distributions by planar and SPECT imaging [10].

Although the potential utility of ^{211}At for targeted radio-therapy has been recognized for more than 30 years, research with this radionuclide has been limited to a few centers and to date, only two studies in patients with ^{211}At -labeled molecules have been reported [11, 12]. The most significant impediment to progress in ^{211}At radiochemistry and clinical application is the limited availability of this radionuclide. As will be discussed in the sections which follow, this does not reflect complexities in production and purification technologies but the limited availability of accelerators with appropriate beam characteristics.

CYCLOTRON PRODUCTION OF ^{211}At

Although it is possible to produce ^{211}At via spallation reactions, either directly or indirectly via decay of ^{211}Rn , these methods are not useful for meeting the demands of routine production because they are not efficient, require particle energies between 160 and 660 MeV (and limited beam intensity) and extensive separation procedures [13]. Currently, the most commonly used method for producing ^{211}At is the bombardment of natural bismuth, generally in metallic form, with α -particles. Although natural bismuth is an ideal target material in terms of expense, obviating the need for procedures to recover and purify the target material, its thermal properties are an issue. Because bismuth has poor thermal conductivity ($7.97 \text{ W}\cdot\text{K}^{-1}\cdot\text{m}^{-1}$) and a low melting point (272°C), it is essential to provide adequate target cooling, particularly when high current production runs are performed.

Target preparation is straightforward with metallic bismuth being fused or vaporized onto an aluminum backing plate, which then may or may not be machined to provide a smooth surface. In order to minimize loss of ^{211}At due to volatilization during the irradiation, the front of the targeted generally is cooled with flowing gas (usually helium) and the back of the target is cooled with flowing water. It should be noted that backing plates made from copper also have been investigated in order to improve thermal conductivity; however, this has been shown to lower ^{211}At isolation yields and result in the production of several radionuclidic impurities including ^{67}Ga , ^{66}Ga , ^{65}Zn and ^{69}Ge [13, 14].

In addition to target cooling, another important constraint in the cyclotron production of ^{211}At is the incident energy of the α -particle beam. The cross sections for the $^{209}\text{Bi}(\alpha, 2n)^{211}\text{At}$ and $^{209}\text{Bi}(\alpha, 3n)^{210}\text{At}$ nuclear reactions have been compiled recently [14] and are presented in Fig. (2). The threshold for the $^{209}\text{Bi}(\alpha, 2n)^{211}\text{At}$ reaction occurs at about 20 MeV and peaks at about 31 MeV; however, one cannot take advantage of the full breadth of the cross section for this nuclear reaction because of concerns about generating 8.3-h half life ^{210}At . This radionuclide is problematic because greater than 99% of its decays results in the production of ^{210}Po , a 138.4-day half life α -particle emitter that can be extremely toxic to bone marrow due to the proclivity of polonium for the bone. The potential lethality of ^{210}Po was illustrated in an unfortunate incident in which Alexander Litvinenko, a former member of the Russian Federal Security Service, was intentionally poisoned with the radionuclide [15].

For this reason, it is advisable to utilize an incident α -particle energy that is below or slightly above the threshold for the $^{209}\text{Bi}(\alpha, 3n)^{210}\text{At}$ reaction, which is about 28.4 MeV [13]. Thick target yields for ^{211}At production have been measured by several research groups for α -particle bombardments performed in the 28–29.5 MeV energy region and yields in the 16.3 to 41 mCi/ $\mu\text{A}\cdot\text{h}$ range have been reported [16–22]. A wide spread of values for thick target yield is not surprising given the steep increase in cross section for the $^{209}\text{Bi}(\alpha, 2n)^{211}\text{At}$ reaction within this small energy range. However, other factors that need to be considered in evaluating these studies are differences in target properties including thickness of the bismuth layer, nature of the target backing with regard to composition and cooling, and whether the measurements were done with an external or internal target.

Perhaps the most useful study from a pragmatic perspective is the work of Henriksen and colleagues [16] evaluating the production of ^{211}At and ^{210}At on an external target as a function of α -particle bombardment energy. Bismuth metal targets of 200 μm thickness on aluminum backing plates were irradiated for 15 min with beam currents of 5 or 10 μA and the energy of the α -particle beam (E_α) was determined using a scattering chamber. Using an E_α of 27.6 MeV, which is below the threshold for the $^{209}\text{Bi}(\alpha, 3n)^{210}\text{At}$ nuclear reaction, as a baseline for comparison, it was found that increasing E_α to 28.6, 29.1, 29.6, and 30.1 MeV increased yields for ^{211}At by about 40%, 70%, 100% and 120%, respectively. The level of ^{210}At relative to ^{211}At at the end of the bombardment at these four E_α also increased, with values of <0.01%, $0.023 \pm 0.006\%$, $0.18 \pm 0.03\%$, and $0.7 \pm 0.1\%$, respectively.

The selection of the ideal incident E_α for ^{211}At production must balance considerations of yield, which will determine cost per MBq, and radionuclidic purity, which will determine suitability for clinical use. While there is some debate as to what level of ^{210}At (and ^{210}Po) could be tolerated and the most relevant way to calculate this, it is clear that it would be reasonable to consider E_α above the putative threshold for ^{210}At production. The toxicity of ^{210}Po has been measured experimentally in many species and elaborate multi-compartmental models for predicting its toxic effects have been developed [15]. A more simplistic approach would be to consider the recommendation of the International

Commission on Radiation Protection for radiation workers of 10 kBq as the annual limit for ^{210}Po intake [23]. Considering the results of Henriksen *et al.* [16], if a clinical dose of ^{211}At were prepared with an E_{α} to 28.6, 29.1, 29.6, and 30.1 MeV, then this limit would be reached at ^{211}At administered activities of 40, 17.4, 2.2 and 0.57 GBq, respectively. To put these doses in perspective, the highest activity level of ^{211}At -labeled anti-tenascin monoclonal antibody used in our clinical study, in which the labeled molecule was given directly into brain tumor resection cavities, was 0.37 GBq and tumor responses were seen at doses half this level [11]. Based in part on these results, we speculate that our planned clinical studies involving administration of ^{211}At -labeled trastuzumab into the intrathecal space for the treatment of neoplastic meningitis and *meta*- ^{211}At]astatobenzylguanidine for the treatment of neuroblastoma via the intravenous route will involve patient doses of ^{211}At up to about 2 GBq. Even at this hypothetical clinical dose, with an $E_{\alpha} = 29.1$ MeV, one could increase yields by a factor of 1.7 and still keep ^{210}Po levels about an order of magnitude below the occupational levels recommended by the ICRP. Although factors such as pharmacokinetics, tissue distribution and elimination of the particular astatinated compound will also play a role, increasing the incident α -particle energy above the threshold for ^{210}At deserves serious consideration.

INTERNAL TARGET SYSTEMS

The production of sufficient amounts of ^{211}At to obtain the levels of ^{211}At -labeled molecules required for clinical studies is difficult with external cyclotron targets because the poor thermal properties of bismuth generally restrict beam currents to a maximum of 15-20 μA . It should be noted that an external target was used to produce 2GBq of ^{211}At for one clinical trial [12]; however, this required irradiation periods of about 8 h, which is not practical for routine use, particularly if the cyclotron in question is heavily utilized for other purposes. One solution to this problem is to utilize an internal target for ^{211}At production and at least three internal target systems designed for this purpose have been described to date [17-19]. A common feature of these systems is a greater target surface area compared with external targets, which contributes to the approximately 4 times higher ^{211}At production yield per $\mu\text{A}\cdot\text{h}$ beam that has been reported when external and internal targets have been compared under similar conditions [18, 19]. In addition, all three internal target systems employ a grazing angle configuration relative to the beam direction to maximize the size and distribution of the beam spot along the target. Spreading the beam out over a larger surface area helps with heat dispersion and allows higher beam currents without melting the bismuth target. The internal target system developed at the NIH has the advantage of being fabricated from disposable materials, significantly decreasing the cost of the target [19]; however, the production rate obtained with this target, 16.3 MBq/ $\mu\text{A}\cdot\text{h}$, is less than half that reported for the other two internal target systems. The maximum ^{211}At activity produced with these internal targets at the time these publications appeared was at least 1.7 GBq in each case, an amount that should be sufficient for preparing initial dose levels envisioned for most ^{211}At -labeled targeted radiotherapeutics.

The highest levels of ^{211}At production reported to date have been achieved with the internal target system that has been in routine use for the past 15 years at our institution and is described in detail in a previous publication [18]. The internal target was designed in collaboration with George Hendry (Cyclotron, Inc.). A curved target configuration was selected in order to maximize beam distribution over the full length of the target through the use of small grazing angles. Electrically-isolated graphite leading- and trailing-edge monitors provide a means for continuously monitoring beam current distribution during cyclotron runs. The back of the target face is water-cooled during irradiations; furthermore, cooling efficiency is maximized by machining cooling fins into the back of the target. Variables which were investigated included target size, backing material composition

(copper or aluminum) and bismuth deposition method on the target surface (electroplating, manual, jet vapor deposition). Beam currents of $>65 \mu\text{A}$ have been used routinely, a vast improvement over the $10\text{--}15 \mu\text{A}$ permitted with external targets. Yields with the preferred conditions – smaller aluminum backing plate configuration and manual deposition of bismuth on the target – were $41 \pm 7 \text{ MBq}/\mu\text{A}\cdot\text{h}$.

This internal target system was utilized to prepare ^{211}At in support of our clinical study evaluating the therapeutic potential of a ^{211}At -labeled antibody in brain tumor patients. A total of 16 production runs were performed with beam currents of $50\text{--}60 \mu\text{A}$ α -particles and irradiation times of 1.5 to 4.5 h [24]. A mean yield of $28 \pm 3 \text{ MBq}/\mu\text{A}\cdot\text{h}$ was obtained with no significant differences in yield seen as a function of beam current or irradiation time. The maximum level of ^{211}At that was produced was 6.6 GBq after a 4-h run at $55 \mu\text{A}$, which to the best of our knowledge, is the highest level of ^{211}At that has been produced to date. It is worth noting that these production runs utilized an incident α -particle beam energy of 28.0 MeV in order to exclude ^{210}At from the preparations. However, work from other research groups [16,17] suggests that by increasing the α -particle beam energy to about 29.5 MeV , it should be possible to almost double ^{211}At production efficiency with this internal target system while producing acceptable levels of ^{210}At .

RECOVERY OF ^{211}At FROM THE CYCLOTRON TARGET

The level of ^{211}At that is available for research and clinical studies is influenced not only by the methods utilized for performing the cyclotron irradiation but also by the procedures for isolating the ^{211}At from the bismuth cyclotron target. The two processes are inextricably related because the ^{211}At separation yield is dependent on the size, thickness and mass of the bismuth target and its backing plate, backing plate material and can also be influenced by the duration and intensity of the irradiation [18]. A variety of methods have been reported for ^{211}At recovery but they generally follow one of two approaches – dry distillation or acid treatment of the target followed by solvent extraction. An excellent review of procedures utilized prior to 1985 has been published [25] and a summary of more recent adaptations of these methods is provided below.

Wet Harvesting Methods for ^{211}At

In this approach, the bismuth target is dissolved in concentrated acid and the ^{211}At activity is extracted into an organic solvent. In a procedure reported by Yordanov *et al.* [26], target dissolution was accomplished using concentrated HNO_3 and the ^{211}At was extracted into either butyl or isopropyl ether. The percentage of ^{211}At recovered from the target was higher with isopropyl ether and decay-corrected yields averaged 93%. However, due to the length of time required for performing these procedures, the average percentage of ^{211}At activity that was available for use at the end of the purification was considerably lower, 72%. This procedure has been utilized successfully by others [27, 28]; however, no additional yield information has been reported. Another approach is to dissolve the target (in this case, Bi_2O_3) in concentrated perchloric acid and then perform solid–liquid extraction employing thiosemicarbazide incorporated onto Amberlite IRC-50 resin [29]. Unfortunately, no yield information was reported. Although wet harvesting methods may be useful for radiochemistry investigations of ^{211}At , particularly when a specific oxidation state is required, this approach is not ideal for processing high levels of ^{211}At because they involve multiple radioactivity handling steps.

Dry Distillation Methods

The most commonly utilized approach for separating ^{211}At from bismuth cyclotron targets is dry distillation in a quartz vessel. A variety of configurations for the distillation apparatus

have been evaluated, with the dimensions of the distillation chamber dependent on the shape and size of the cyclotron target and backing plate. All procedures involve a distillation temperature above the melting point of bismuth, with most being performed in the 650-800°C range. In some cases, the bismuth metal is removed from the aluminum backing plate before commencing the distillation [30]; however, this additional step must be done with care to minimize loss of activity and contamination of the workspace. Generally, the duration of the distillation is 30 min or less because incremental gains in yield with longer distillation periods are not that significant because of decay of ^{211}At during the procedure. Effective trapping of ^{211}At can be achieved by combining a gentle flow of carrier gas - generally nitrogen [30] or argon [24] - with vacuum evacuation of the distillation apparatus.

Trapping of the ^{211}At after volatilization from the cyclotron target has been accomplished using silica columns [31], bubbler traps [32], and capillary tubing cryotrap [30]. A problem in the past with dry distillation procedures for isolating ^{211}At from cyclotron targets is the wide variation in distillation yield from run to run. The distillation yield that we obtained with a bubbler trap containing chloroform was $67 \pm 16\%$ for 16 therapy-level production runs [24]. We have now switched to a capillary cryotrap fabricated from polyetheretherketone (PEEK) tubing as described by Lindegren and colleagues [30]. The set up is as described [24] except that the current distillation device uses a PEEK capillary loop (1.6-mm tubing, 1-mm inner diameter, 152-cm length) instead of the glass vials that were used in the past for trapping the ^{211}At activity [33]. One reason for this change was to delay the time at which the ^{211}At first was exposed to the solvent in order to minimize problems related to radiolysis of the solvent by the cumulative effect of ^{211}At α -particles [34]. This revised system has been reliable and yields for the recovery of ^{211}At from the cyclotron target have been about 70%.

FACTORS INFLUENCING LIMITED AVAILABILITY OF ^{211}At

The potential advantages of ^{211}At for targeted α -particle radiotherapy have been recognized for about 40 years and the encouraging results obtained with a wide variety of ^{211}At -labeled compounds have provided further evidence in support of its use for in cancer treatment. In a survey of European nuclear medicine professionals conducted in 2005, the therapeutic radionuclides of greatest interest were ^{211}At and ^{67}Cu [35]. Perhaps the most significant impediment to the clinical application of ^{211}At -labeled targeted radiotherapeutic agents is the limited supply of this radionuclide. This perspective is supported by the conclusions of two recent analyses on radionuclide supply needs for medical applications in the United States, which emphasize the importance of developing the infrastructure required to make ^{211}At available for research and clinical trials [36, 37].

From the previous sections of this paper, it is clear that the limited availability of ^{211}At does not reflect complexities in production and purification technologies, which are quite simple. Moreover, the intrinsic cost of producing ^{211}At is quite low, particularly when compared to the cost of other potential α -particle emitters for cancer therapy such as ^{225}Ac . The cost of producing ^{211}At can be estimated using expenses and production capabilities at our institution as an example. With our internal target system, 150-175 mCi of ^{211}At has been produced after a 4-h cyclotron bombardment [24]. The amount currently charged for performing cyclotron irradiations at Duke University Medical Center is \$400 per hour and the all inclusive cost for fabrication of the bismuth cyclotron target and aluminum backing plate is about \$75. Based on these assumptions, the cost for producing ^{211}At is only about \$10 per mCi. If one assumes a 67% yield in isolating this radiohalogen from the cyclotron target [24] and a one half life time period for processing and physical decay, this results in an approximate cost of \$30 per mCi to a remote user. In order to put this in perspective, a useful benchmark is the cost of ^{123}I , which has a reasonably similar half life (13.2 h). In

2010, the price for ^{123}I was about \$70 per mCi when ordered in 5-20 mCi allotments. Thus, even if one factors in a profit margin of 100%, the cost of ^{211}At is less than that of ^{123}I , an imaging radionuclide that is currently available from multiple commercial sources.

By far the most important factor influencing the supply of ^{211}At is the limited availability of accelerators that are capable of generating an 28-MeV α -particle beam in the intensities needed to produce useful levels of ^{211}At . Given the considerable interest in ^{211}At -labeled radiopharmaceuticals for cancer treatment and the low intrinsic cost of ^{211}At production, it might be reasonable to ask why commercial entities have not become involved. The simple explanation is that cyclotrons for commercial radionuclide production are optimized for high current proton irradiations and few if any could be modified to have α -particle beam capabilities. This is an important distinction in explaining differences in the availability of ^{123}I and ^{211}At – in contrast to the ^{211}At , existing equipment could be utilized to meet emerging needs for ^{123}I production, which is generally accomplished commercially via the $^{123}\text{Te}(p,n)$ and $^{124}\text{Te}(p,2n)$ reactions.

In all likelihood, initiation of a ^{211}At production program in the commercial sector would require the purchase of a new cyclotron or linear accelerator with high-current α -particle beam capability. Unfortunately, an investment of this magnitude is not likely for at least two reasons. First, there are not many other radionuclides of commercial interest that require an α -particle beam for their production and most of these can also be produced by proton-induced reaction channels [38]. This problem can be ameliorated if the accelerator is a multi-particle machine; however, this is not ideal because of the loss of productive beam time during particle switches. In addition, the proton (and deuteron) beam can exploit the advantages of negative ion technology (low activation of machine components, high efficiency stripper extraction and dual beam capability) while the α -particle beam is limited to positive ion technology. And second, justification of an investment in an accelerator for commercial ^{211}At production must be based on convincing evidence that the demand for ^{211}At will be large and sustained enough to yield a reasonable profit. It is difficult to envision this occurring without the demonstration of clinical efficacy of at least one ^{211}At -labeled targeted radiotherapeutic, most likely, in a disease with a relatively high incidence such as breast, lung or prostate carcinoma. Unfortunately, the conundrum confronting the ^{211}At field is that commercial supply of ^{211}At awaits the demonstration of clinical efficacy; however, the demonstration of clinical efficacy requires a reliable supply of ^{211}At .

A POSSIBLE SOLUTION TO THE ^{211}At SUPPLY PROBLEM

Although the ideal solution to the limited availability of ^{211}At probably would be for this radionuclide to be available commercially, this is unlikely to occur in the foreseeable future for the reasons discussed in the previous section. Two scenarios have been proposed recently for improving the availability in the United States of ^{211}At and other radionuclides of therapeutic interest [36,37]. The first would be to build and operate a National Biomedical Accelerator and Radiochemistry Facility that would be charged with the task of supplying a range of radionuclides of interest at a reasonable cost. This concept has been proposed multiple times in the past 20 years and has been considered by a variety of federal agencies and nonprofit foundations; however, substantive progress has not been made due in large part to an estimated cost of the cyclotron and associated building in the range 50-75 million dollars. Given the current status of the world economy, this is not considered to be a viable option at this time.

The second approach is to utilize existing cyclotrons to create a consortium or network of machines that can be utilized to address ^{211}At production needs. Most of the cyclotrons throughout the world that are capable of ^{211}At production are older machines that were

originally built for other purposes such as nuclear physics research. With the decline in research funding in this area, the number of accelerators with medium energy α -particle beams is decreasing. Two examples of this trend within the United States are the decommissioning of the 60-in. cyclotrons at Argonne National Laboratory and Brookhaven National Laboratory, both of which were used in the past for ^{211}At production and research.

Fortunately, many other cyclotrons remain in all parts of the world that could be utilized for ^{211}At production and this may be an attractive possibility to local authorities because the majority of these machines are underutilized and underfunded. In order to explore the feasibility of this strategy, we have evaluated the characteristics of the 262 cyclotrons from 39 countries compiled in a report by the International Atomic Energy Agency [39]. Astatine-211 production capability was described as low, medium or high based on the maximum α -particle energy and intensity listed by the cyclotron facility. An E_{α} of 25-28 MeV with a maximum beam current of 1-5 μA was considered to provide low production capacity – sufficient to supply the levels of ^{211}At needed for radiochemistry research and cell culture studies. An E_{α} of 25-28 MeV with a maximum beam current of 5-10 μA was considered to provide medium production capacity – sufficient to supply the levels of ^{211}At needed for therapy experiments in animals and the preparation of single, low activity level patient doses. An E_{α} of at least 28 MeV with a maximum beam current greater than 10 A was considered to provide high production capacity – sufficient to supply the levels of ^{211}At needed for multiple clinical doses of ^{211}At -labeled therapeutics.

Based on these criteria, 36 cyclotrons were identified in the IAEA report as having α -particle beam characteristics consistent with the production of ^{211}At , with the majority of these potentially capable of generating sufficient activity levels to permit at least single patient doses of ^{211}At -labeled targeted radiotherapeutics. As summarized in Tables 1-3, potential cyclotrons for ^{211}At production exist in 20 countries, with Germany and the United States having the largest number of potential production sites. However, it is important to note that at the present time, only a few of these cyclotrons routinely produce ^{211}At on a routine basis (Rigshospitalet in Denmark, and the University of Washington, National Institutes of Health, and Duke University in the United States). In addition, there are about 10 other accelerators, including cyclotrons in China, Czech Republic, Russia, France, Germany, Italy and Norway that have been used in the past for ^{211}At production.

The practical significance of this particular list of potential ^{211}At production sites may be compromised somewhat by the decommissioning of some of these machines during the 5 years since the data for the IAEA report was compiled and the accuracy of the beam characteristics described in the report. On the other hand, there are other older cyclotrons not mentioned in the report such as the JSW30 at the University of Pennsylvania as well as newer cyclotrons including those in France (IBA C70; Arronax, Nantes) and Germany (IBA C30; Forschungszentrum Jülich) that have or will have ^{211}At production capability. It is likely that several machines that are not routinely producing ^{211}At at the current time have sufficient beam time available for this purpose. However, some of these cyclotrons are in hibernation mode and may not have sufficient local expertise remaining in cyclotron targetry and radiochemistry to embark on a ^{211}At production program. One solution would be to establish a regional consortium of institutions that could share ^{211}At production technology, ultimately developing an automated system such as the Compact Solid Target Irradiation System (COSTIS) and Tellurium based Radioiodine production MOdule (TERIMO) devices developed for ^{124}I production and purification, respectively [40]. The critical issue will be to find a mechanism for funding such a project. With the initiation of collaborative projects such as Targeting Alpha-Particle Emitting Radionuclides to Combat Cancer (TARCC) by the European Commission, this may not be beyond the realm of possibility.

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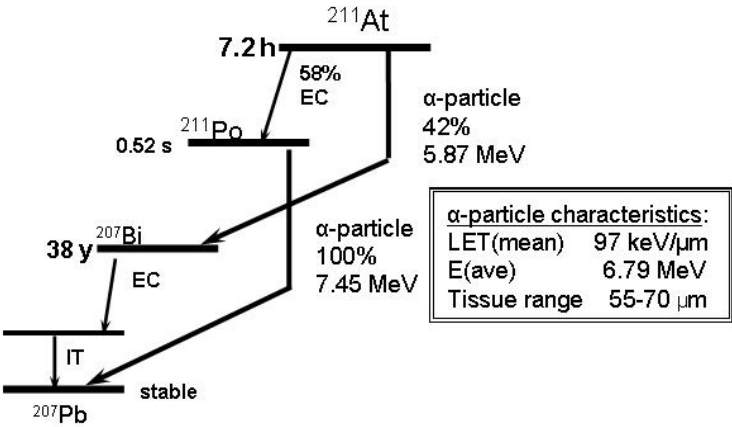
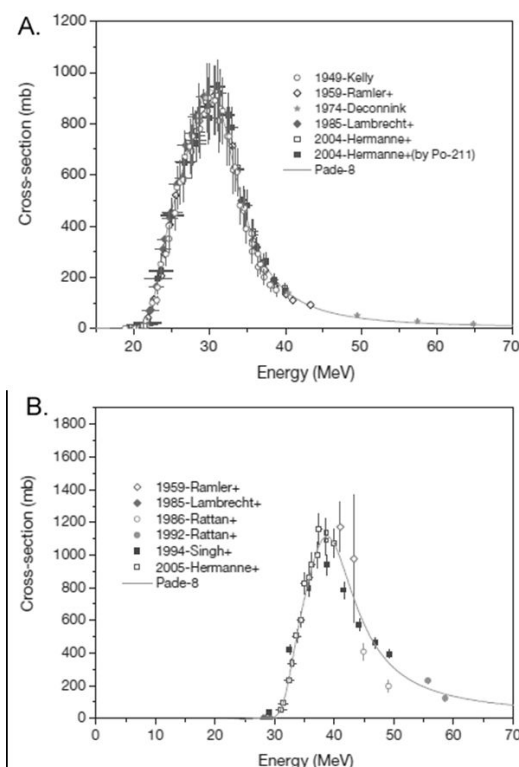


Fig. (1). Simplified scheme illustrating double-branched decay of ^{211}At .

**Fig. (2).**

Excitation functions for α -particle-induced reactions on natural bismuth targets; A) $^{209}\text{Bi}(\alpha, 2n)^{211}\text{At}$ reaction and B) $^{209}\text{Bi}(\alpha, 3n)^{210}\text{At}$ reaction. Cyclotron Produced Radionuclides: Physical Characteristics and Production Methods, Technical Reports Series Number 468, International Atomic Energy Agency: Vienna, **2009**, pp. 33-40 with permission from the IAEA.

Table 1

Potential Sites for ^{211}At Production in Europe

Location	Organization	Maximum α -Particle Energy (MeV)	Maximum α -Particle Intensity (μA)	Capacity
Brussels, Belgium	Vrije Universiteit	43	20	Medium
Ghent, Belgium	University of Ghent	29	60	High
Louvain, Belgium	Catholique Universiteit	110	20	High
Rež, Czech Republic	Nuclear Physics Institute	40	3	Low
Copenhagen, Denmark	Rigshospitalet	32	30	High
Nice, France	Centre Antoine Lacassagne	65	40	High
Orleans, France	CNRS/CERI	50	5	Medium
Dresden, Germany	Forschungszentrum Rossendorf	28	20	High
Essen, Germany	Institute for Medical Radiation Physics	28	50	High
Jülich, Germany	Forschungszentrum Jülich	28	20	High
Karlsruhe, Germany	Forschungszentrum Karlsruhe	104	50	High
Hamburg, Germany	Universitätsklinikum Hamburg-Eppendorf	30	?	?
Hannover, Germany	Medizinische Hochschule Hannover	35	20	High
Ispra, Italy	European Commission Joint Research Center	39	30	High
Amsterdam, Netherlands	Vrije Universiteit	32	10	Medium
Oslo, Norway	University of Oslo	35	20	High
Krakow, Poland	Henryk Niewodniczański Institute of Nuclear Physics	60	5	Low
Bucharest, Romania	National Institute for Physics and Nuclear Engineering	27	10	Medium
Moscow, Russia	Kurchatov Institute of Atomic Energy	60	20	High
Tomsk, Russia	Tomsk Polytechnic University	28	55	High
London, United Kingdom	Hammersmith Imanet	40	60	High

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Table 2

Potential Sites for ²¹¹At Production in North and South America

Location	Organization	Maximum α-Particle Energy (MeV)	Maximum α-Particle Intensity (μA)	Capacity
Rio de Janeiro, Brazil	Instituto de Engenharia Nuclear	28	25	High
Bethesda MD, USA	National Institutes of Health	30	90	High
Durham NC, USA	Duke University	30	100	High
Ann Arbor MI, USA	University of Michigan	30	90	High
College Station TX, USA	Texas A & M University	70	1	Low
Houston TX, USA	University of Texas at Houston	40	30	High
Seattle WA, USA	University of Washington	47	70	High
Davis CA, USA	University of California at Davis	90	40	High

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Table 3

Potential Sites for ²¹¹At Production in Asia

Location	Organization	Maximum α-Particle Energy (MeV)	Maximum α-Particle Intensity (μA)	Capacity
Beijing, China	Beijing Normal University	30	100	High
Calcutta, India	Variable Energy Cyclotron Centre	26	200	Medium
Gunma, Japan	Japan Atomic Energy Research Institute	100	7	Medium
Sendai, Japan	Cyclotron and Radioisotope Center	50	5	Medium
Seoul, Republic of Korea	Korea Atomic Energy Research Institute	51	Low current	Medium?
Almaty, Kazakhstan	Institute of Nuclear Physics	50	100	High
Riyadh, Saudi Arabia	King Faisal Specialist Hospital and Research Centre	30	90	High