Is ^{211}At Really Happening?

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Beyond the ^{177}Lu-based radiopharmaceuticals targeting somatostatin receptor and prostate-specific membrane antigen, there are new therapeutic radiopharmaceuticals that can potentially reach the market within the next 10 y. These molecules are labeled with ^{67}Cu, ^{90}Y, ^{131}I, ^{161}Tb, ^{188}Re, ^{211}At, ^{212}Pb, or ^{225}Ac (*1*,*2*). No other radionuclides are likely to reach the market within this time frame, as both developing the drug and building the infrastructure to produce these radionuclides on an industrial scale will take more than 10 y. Although earlier generation radiotherapeutic radionuclides including ^{89}Sr, ^{153}Sm, or ^{223}Ra may continue to be available in already approved drugs, they will only be found in new generic formulations, not as part of novel, original radiolabeled entities. As described previously, the access to industrial-scale quantities of ^{225}Ac (*3*) and ^{212}Pb (*4*) over this same time frame is nearly secured, as major pharmaceutical companies with significant financial resources have committed to investing in large-scale production facilities and an associated network.

^{211}At stands out as a third radionuclide worth considering. Although being explored for years by a small group of dedicated scientists, it is just starting to reach a level of development that would attract significant investor interest. However, even if ^{211}At-radiolabeled drugs have a strong potential to reach the market by 2032–2036, this will happen only under certain conditions outlined in the following.

α-EMITTING RADIONUCLIDE WITH ORIGINAL PROPERTIES

^{211}At is an α-emitter that decays with a 7.21-h half-life into ^{211}Po (58.3%, through an electron conversion process) and ^{207}Bi (41.7%, with an α-emission at 5,870 keV). ^{211}Po transforms through a 0.52-s half-life process into stable ^{207}Pb (100%) with a 7,450 keV α-emission, also with x-ray emission at 77–92 keV that could be used for imaging. From the second decay branch, ^{207}Bi transforms into ^{207}Pb with a simple electron capture decay with a half-life of 32.9 y. Concerns were raised about the presence of this long–half-life isotope in the patient and their waste. However, the low level of risk was explained by the high dilution over time (*5*). Unbound ^{211}At also accumulates in the thyroid (as astatine behaves like iodine), as well as in the stomach, spleen, and lungs. This can be controlled in the same way as accidental intake of ^{131}I, by presaturating the thyroid with nonradioactive iodine (*6*).

Astatine belongs to the halogen family and shares similar properties with iodine, such as chemically forming a covalent bond with carbon atoms. Although additional chemistry development was challenging to stabilize this quite labile bond, significant progress has been made (*7*,*8*). This covalent bond offers an advantage over metals, as ^{211}At does not need a large chelating agent such as ^{177}Lu or ^{225}Ac. The smaller size of this radionuclide substructure allows ^{211}At-labeled small molecules or peptides to cross the blood–brain barrier, making them well-suited for early-stage brain tumor therapies.

Additionally, in parallel to the first α-decay leading to ^{207}Bi, ^{211}At is also an Auger electron emitter, which may provide additional advantages over other α-emitters. The future of nuclear medicine may evolve in cocktail therapies, which involve combining chemotherapy with vectorized radiotherapy, using mixtures of α- and β-emitters, or even combining α or β with Auger or conversion electron emitters. In the case of ^{211}At, the simultaneous emission of α-particles and Auger electrons may show superiority to other radionuclides, despite its short half-life. Similarly, in preclinical trials, ^{161}Tb has already shown superiority over ^{177}Lu because of its additional Auger electron emission (*9*). Further improvements in efficacy could be achieved by combining ^{211}At-labeled drugs with their ^{131}I analogs (a β-emitter with a long half-life of 8.02 d) or even their ^{123}I analogs (an imaging radionuclide, but also an Auger electron emitter with a short half-life of 13.27 h). One goal could be to label the same molecule with both an atom of ^{123}I and an atom of ^{211}At to achieve high efficacy in a single drug. This approach would be effective only with molecules that have proven to internalize, as Auger electrons are highly efficient only when they stay close to the DNA of the tumor cell. This is a new area to explore.

In the future, millions of patients could be treated by radiotherapeutics, most of them on an outpatient basis, because of the limited capacity of existing hospital facilities. Treating patients with long–half-life radionuclides may not be posing a risk to the patients themselves (until proven otherwise), but the increasing radioactivity released into the environment may raise concerns for public health and ecological authorities and may be challenged (*10*). In this context, short–half-life radionuclides such as ^{211}At and ^{212}Pb will show an advantage, if only from a simple marketing point of view. Although this issue will not jeopardize the short-term development of ^{177}Lu- and ^{225}Ac-labeled drugs, anticipating cultural changes should already favor the development of next-generation drugs labeled with ^{211}At or ^{212}Pb.

EASY BUT STILL EXPENSIVE PRODUCTION ROUTE

^{211}At is produced via the [^{209}Bi(α,2n)^{211}At] reaction in a cyclotron or linear accelerator, requiring an average energy of 28–29.5 MeV. This precise and low energy helps avoid the production of the impurity ^{210}At (half-life, 8.1 h, decaying into ^{210}Po, half-life, 138 d) through the [^{209}Bi(α,3n)^{210}At] route at 32 MeV. By staying with an

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internal α-beam energy below 29.5 MeV and running the accelerator for about 4 h, no ^{210}At impurity is observed. Purification is performed via dry distillation, liquid–liquid separation, or solid-phase extraction.

New technologies involving linear accelerators (Nusano) could reach higher yields but will be more expensive. Eventually, there is no risk of shortage of ^{209}Bi, the natural target material which is inexpensive and offers opportunities in scalable target manufacturing.

As an alternative, ^{211}At can also be produced using a ^{211}Rn/^{211}At generator. ^{211}Rn has a half-life of 14.6 h and decays into ^{211}At (73%) and ^{207}Po (27%). ^{211}Rn can be produced by spallation of ^{227}Th with high energy protons [^{227}Th(p,2α)^{211}Rn], a method explored by TRIUMF in Canada, or by irradiating ^{209}Bi with lithium ions [^{209}Bi(^{7}Li,5n)^{211}Rn], proposed as early as 1980 in the United States and also explored by GANIL in France.

However, neither of these research units has initiated the development of an industrial tool based on these methods.

AN IMPORTANT EXPERT COMMUNITY AND AN ACADEMIC NETWORK

Unlike ^{67}Cu, ^{117m}Sn, or even ^{161}Tb, ^{211}At already benefits from a large and organized global community of experts dedicated to enhancing access to this radionuclide and working to coordinate all sites capable of producing preclinical and clinical doses for accelerating drug development (COST NoAr (*11*)). As a counterexample, such a community has never existed for ^{166}Ho, which allowed for the development of the strongly industry-supported ^{177}Lu, a radionuclide with very similar properties, bringing at the same time the development of ^{166}Ho-labeled drugs to a full stop.

This promising situation has sparked interest from industries, particularly cyclotron manufacturers (IBA, ACSI, SHI) who have developed, first, multipurpose (multiparticles) and, more recently, specialized tools for the production of pure ^{211}At.

Among the approximately 30 identified cyclotrons operating worldwide and that have the beam energy to produce ^{211}At, only 13 are equipped and capable of producing ^{211}At batches on request, with much of such equipment being very old cyclotrons unsupported by the original manufacturer anymore. These cyclotrons are not yet in routine production cycles, and most of them will never be. A review published in 2021 (*12*) describes all potential ^{211}At sources. Unfortunately, all these centers except for 3 (Ionetix, Alpha Nuclide, and Nusano, which are all under construction) are either academic or government-owned cyclotrons.

The pharmaceutical industry will invest in ^{211}At only if there is a guarantee of daily supply, at least 5 d a week, all year around, once a radiolabeled drug reaches the market. None of the existing research cyclotrons can meet the demand for such a reliable supply. These existing centers are nevertheless crucial for developing production technologies, improving labeling methods, and providing doses for clinical trials, but they cannot be used for future routine production. Investors will fund ^{211}At projects only when long-term supply solutions are guaranteed. Developers will initiate programs in this direction when they have access to funds. This cycle of interest was up to now limiting the development of new ^{211}At-labeled drugs. At this stage, a program has been initiated from a network perspective in Japan, but it is far from being adapted for large-scale production and is not intended for expansion beyond this country at this time.

NEW DRUGS UNDER DEVELOPMENT

Even though most research groups are merely adapting ^{211}At to existing ^{177}Lu or ^{225}Ac analogs, some newcomers and startups are genuinely considering the advantages of ^{211}At over other α-emitters. More than 30 different ^{211}At-labeled molecules are reported to be under development, with 10 having reached the clinical stage (*2*). As long as these molecules are developed solely within the academic environment and lack financial support from industrial funds, their future remains highly uncertain.

However, recently, radiopharmaceutical companies such as Affibody, Alpha Fusion, Atonco, Iodax, Radiopharm Theranostics, Solve Therapeutics, Telix Pharmaceuticals, Tetrakit Technologies, or Z-Alpha Therapeutics have decided to invest in specific ^{211}At-labeled molecule development programs and have raised money for this purpose. The indications of interest target prostate cancer but more often orphan diseases such as bladder cancer, glioblastoma, triple-negative breast cancer, and thyroid cancer. The replication of existing approaches (*13*) based on molecules labeled with ^{177}Lu or ^{225}Ac (e.g., targeting prostate-specific membrane antigen or somatostatin receptor) does show limitations due to the highly competitive environment, highly reducing interest from investors.

PRODUCTION TOOLS WITH LIMITED CAPACITY

The relative limited interest from the biopharma industry in ^{211}At-labeled molecules is directly linked to the absence of a reliable, worldwide industrial-scale source of the radionuclide. On the basis of the information provided so far, it is possible to roughly evaluate the yearly production capacity of a single production site and estimate the number of sites needed to cover the main markets.

If an optimized cyclotron production yield of 400 mCi (14.8 GBq) is assumed at the end of a 4-h irradiation period with the current limited to 100 μAe on target (up to 400 μAe was tested and a maximum of 200 μAe recommended at the cyclotron itself (*14*)), followed by distillation yields reaching 88% non–decay-corrected (Atley Solutions) (*15*), an optimized 75% radiolabeling yield, and accounting for 2 half-lives lost between the end of irradiation and calibration time, the remaining available amount averages 66 mCi (2.4 GBq) of radiolabeled drug per batch. Ideally, a cyclotron could produce up to 6 batches per day, that is, 6 × 66 mCi is 396 mCi (14.6 GBq). To stay on the safe side, Alpha Nuclide recommends working for the time being with lower current compensated by 6 h of irradiation and a maximum of 4 batches per day, resulting in a capacity of 260 mCi (9.6 GBq) of radiolabeled drug at calibration per day. All these figures are considered to be conservative, as the potential of improvement remains high and could be multiplied by a factor of 2–4. Shorter distribution distances will also increase the capacity.

The dose to be injected to a patient is still uncertain at this stage of development and could vary significantly. However, based on current clinical trials, a single dose of 10 mCi (370 MBq) appears to be an acceptable average. Initial estimates set the limit between 7 and 15 mCi (260–555 MBq).

Therefore, a cyclotron could produce the equivalent of 26 doses per day, but since at least 1 dose per batch will be needed for analytic purposes, only 22 doses can be allocated to patients. If operating 5 d a week, that is, 260 d a year, this would correspond to an annual production capacity of about 5,720 doses per site per cyclotron. Indeed, an improvement of up to 2 times this figure could also be expected.

By considering the situation from a different perspective, the average period of 2 half-lives becomes the basis for estimating the number of centers needed to cover the major markets. These 2 half-lives account for the necessary time for target exchange and extraction, radionuclide purification, radiolabeling, and dispensing, which takes about 2–4 h. The remaining 10 h correspond to the average time for ideally overnight shipment to the final customer and injection to the patient the following morning.

Indeed, a single center could supply all hospitals located within a 10 h transport distance. The shorter the distance, the better the ratio of doses to batch size. A network of 5 cyclotrons to cover the North American market, another 5 for Europe, and 2 additional cyclotrons for isolated interesting markets such as Australia would be a realistic initial approach. Such a network of 12 cyclotrons would have a production capacity of 68,000 doses per year, which still presents an interesting business case but also raises several new points and limitations:

- From a very optimistic perspective, ^{211}At could prove to be largely superior to ^{225}Ac, up to a potentially first single dose treatment, but this, obviously, will need to be demonstrated in comparative clinical trials. So, based on a more realistic 3 doses per full treatment, the network will be able to treat about 23,000 patients a year. This is quite small for a large indication such as prostate cancer but highly realistic when targeting an orphan disease.
- Investors push for global market development. Considering the current sales price of radiotherapeutics, which is now similar to that of chemotherapeutics, single doses can be expected to sell for around $40,000 in the United States and half of it in Europe. With $30,000 on average, a market of 68,000 doses could generate over $2 billion in revenue at its peak, making it a blockbuster despite the low production level.
- However, this means that a network of 12 cyclotrons can only be dedicated to a single drug, and a similar network will need to be built for each new drug. This is advantageous for a company that targets a fully integrated production.
- Each production site requires a dedicated 30-MeV α-beam accelerator estimated to cost between $5 and $7 million. This cyclotron must be integrated into a simplified structure (dedicated to ^{211}At only, mimicking the FDG-only PET centers) costing less than $15 million. With a full cost per unit of around $20 million, the total investment for a network could remain below $250 million.
- This initial investment should be compared with the potential yearly billion-dollar revenues, which show that if the network's capacity is insufficient, an additional investment of "only" $250 million would be enough to potentially double revenues. The adaptation to larger population indication will need a proportional increase of the size of the network and the investment.

CONCLUSION

^{211}At offers several advantages: it emits short–half-life α-particles along with Auger electrons, and its chemistry involves covalent bonding, which allows for the exploration of indications limited when using chelated metals (e.g., brain). Over the past 15 y, a strong community of experts has significantly improved radionuclide production capacity, labeling yields, and the chemical stability of final drugs. Despite the low production capacity of cyclotrons, investing in a network of a dozen of sites makes economic sense. It is highly likely that as many networks of 30 MeV α-cyclotrons as future drugs on the market, and companies linked to these drugs, will be built.

Ultimately, it would make more sensible to dedicate ^{211}At to original approaches and orphan drug indications, as competition with existing drugs (e.g., for prostate cancer, neuroendocrine tumors) would be very challenging and complex. It is also recommended to focus on indications that are not already the primary targets of companies developing ^{177}Lu- or ^{225}Ac-labeled compounds. Recent announcements are set to significantly transform the landscape and outlook of the industry. The company Alpha Nuclide is already starting to build its second site in China and is considering a third one in the United States. The companies Framatome and IBA announced the inception of a fully ^{211}At-dedicated network of industrial cyclotron–equipped production centers (*16*). Companies such as ACSI, Atley Solutions, IBA, Ionetix, and Nusano are continuing to develop improved production tools or new ^{211}At-related technologies. Furthermore, the accelerate.eu and Thera4care programs (*17*) have secured substantial European funding to advance technologies related to ^{211}At. Collectively, these investments mark a significant milestone, affirming that ^{211}At will really happen.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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