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ASTATINE-211 AS AN EMERGING RADIOISOTOPE FOR TARGETED ALPHA THERAPY (TAT)

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Abstract. *Cancer treatment presents complex challenges, necessitating the exploration of innovative approaches for diagnosis and therapy. Among emerging prospects, Radiopharmaceutical Therapy (RPT) using α- emitting radionuclides has gained notable attention. This article provides an overview of the literature on Targeted Alpha Therapy (TAT), explicitly focusing on astatine-211 (^{211}At). It discusses methodologies for labeling ^{211}At, along with the associated challenges, to contribute to a deeper understanding of its potential role in TAT. The physical properties of ^{211}At make it a promising candidate for treating micrometastases and disseminated tumours. Its high linear energy transfer and limited tissue range minimize the damage to healthy cells. The review explores the implications of the ongoing research project NOAR-COST focused on Network for Optimized Astatine labeled Radiopharmaceuticals. Overall, the article underscores the growing significance of the α-emitting radionuclides in cancer therapy and provides an overview of the clinical studies, highlighting the potential for ^{211}At to become a pivotal component of TAT.*

Keywords: *α- emitting radionuclides, astatine-211, NOAR-COST, Targeted Alpha Therapy (TAT)*

1. INTRODUCTION

There is a persistent need for advancement in addressing the complexities of diagnosing, managing, treating, and predicting cancer. Cancer treatment is intricate due to its multifaceted nature, which varies depending on the type of cancer, its stage, and the patient's overall health. Treatment modalities may include surgical intervention, chemotherapy, radiation therapy, targeted therapies, immunotherapy, hormonal therapy, laser therapy, etc [1]. An emerging perspective in cancer treatment is Radiopharmaceutical therapy (RPT), which involves the systemic or locoregional administration of radioactive atoms to target tumours. This therapeutic modality is used with approved compounds such as Xofigo®(^{223}Ra), Lutathera® (^{177}Lu), and Pluvicto® (^{177}Lu) in small clinical trials in Europe, USA, and Japan [2].

There is no ideal radionuclide for therapy, and the selection depends on the physical half-life, radiation energy, daughter products, production method, and radionuclide purity [3]. Radionuclides that emit alpha (α) or beta (β^-) particles, as well as Auger electrons, are suitable for therapeutic purposes, but mainly used are α- and β-emitting radionuclides. β-particles are electrons emitted from the nucleus (negatively charged particles) and are commonly used due to their easy availability and established therapeutic benefits. Some of the β-emitting radionuclides (e.g., ^{177}Lu, ^{131}I, $^{186/188}$Re) also emit gamma (γ) photons, which could be used for imaging purposes and make them appropriate candidates as theranostic [4]. They have low linear energy transfer (LET) and a relatively long path up to 12 mm. α-particles, on the other hand, are composed of helium nuclei (two protons and two neutrons) emitted from the nucleus of a radioactive atom. They have high LET and shorter path lengths, up to 100 μm [5].

Although α-radionuclides are not widely used and face certain limitations, their potential in developing Targeted Alpha Therapy (TAT) offers new opportunities for advancement. TAT involves using various vector molecules such as antibodies, peptides, or small molecules that target the cancer, labeled with α-emitting radionuclides [6]. The first clinical application of TAT was observed in 1995, with ^{213}Bi in patients with leukaemia, when the pharmacokinetics and dosimetry were determined [7]. Ongoing interest in the development of novel radiopharmaceuticals for TAT is evident from the multitude of active clinical trials (75) and preclinical research undertakings [8], [9]. Predictions suggest that TAT may become the standard oncological treatment [10].

Eychenne et al. highlighted several radionuclides as promising radionuclides for TAT: actinium-255 (^{225}Ac), astatine-211 (^{211}At), bismuth-212 (^{212}Bi), bismuth-213 (^{213}Bi), lead-212 (^{212}Pb), radium-223 (^{223}Ra), and thorium-227 (^{227}Th) [11]. Additionally, other radionuclides could potentially be used for TAT. Still, the use is limited due to several factors: either their short or excessively long half-lives, unexplored chemistry, or complex decay pathways [12].

This article provides an overview of the literature on TAT, explicitly focusing on ^{211}At. By exploring the methodologies for labeling with ^{211}At and addressing the associated challenges, this review will contribute to a deeper understanding of its potential role in TAT. A

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project related to ^{211}At research will be discussed and analysed to determine its implications for the knowledge and usage of this particular α-emitting radionuclide.

2. Therapy using Alpha radionuclides

The physical properties, such as short range in tissue (50–80 μm) and high LET (80–100 keV/μm), make the α-emitting radionuclides particularly suitable for disseminated micrometastasis, residual cancer cells after surgical debulking, and solid tumours treatment [13]. The high LET of α-emitters induces irreversible DNA damage, primarily through double-strand breaks (DBSs), with 100 times greater cytotoxic potency than β-emitters. In the relatively short path length, α-emitters deposit very high localized radiation, thus minimizing the radiation exposure to nearby healthy tissue [14].

Energy transfer of α-emitters occurs via a direct pathway targeting DNA and other biomolecules or an indirect pathway, producing reactive oxygen species (ROS) like hydroxyl radicals (•OH) that subsequently interact with various biomolecules [15]. The destructive power of α-particles far exceeds that of β-particles because they deposit 1500 times more energy per unit path length [16]. Properties such as the high LET in a short range, irreparable DNA damage, and the similar diameter of metastatic tumour cells with the short range of α-particles, make them a better choice for treating micrometastasis compared to β-emitters [17], [18].

Among the long list of α-emitters (around 100), a limited number, including those listed in Table 1 [19], could be a strong candidate for development and eventual introduction into clinical practice. This is primarily due to their suitability and effectiveness for treating micrometastases, leukemia, lymphomas, gliomas, and melanoma. However, supply limitations and high costs are notable issues to consider [20].

Table 1. List of α-emitting radionuclides candidates for TAT

α-emitting radionuclide	Physical Half-life	Particle emitted per decay	Maximum energy [keV]	Mean energy of α-particles emitted per disintegration [MeV]	Associated emissions	Occurrence [%]
^{225}Ac	10 d	4α, 2β$^-$	5.830	8.83	α, γ, Auger, β$^-$	α (100%)
^{211}At	7.21 h	1α, 1EC	5.867	6.79	α, γ, EC	α (41.8%)
^{212}Bi	60.6 min	1α, 1β$^-$	5.870	7.80	α, γ, Auger, β$^-$	α (36%)/ β$^-$ (64%)
^{213}Bi	45.6 min	1α, 2β$^-$	6.051	8.37	α, γ, Auger, β$^-$	α (2.2%)/ β$^-$ (97.8%)
^{212}Pb	10.6 h	1α, 2β$^-$	570	6.05	α, γ, Auger, β$^-$	β$^-$ (100%)
^{223}Ra	11.4 d	4α, 2β$^-$	5.871	5.7	α, γ, Auger, β$^-$	α (100%)
^{149}Tb	4.1 h	1α, 1β$^+$	3.967	3.97	α, γ, β	α (17%)
^{227}Th	18.7 d	5α, 2β$^-$	6.038	5.9	α, EC, β$^-$	α (100%)

The early stages of TAT in human clinical trials begin with the utilization of [^{213}Bi]CHX-A-DTPA-HuM195, a labeled anti-CD33 antibody, for treating myeloid leukaemia [21]. ^{213}Bi-labeled compounds have been employed for treating various conditions such as lymphoma (^{213}Bi-anti-CD20-mAb radiopharmaceutical) [22], melanoma (^{213}Bi-anti-MCSP-mAb radiopharmaceutical) [23], bladder cancer (^{213}Bi-anti-EGFR-mAb) [24], glioma (^{213}Bi-Substance P) [25], and neuroendocrine tumours (^{213}Bi-DOTATOC) [26].

In the United States, several clinical trials have been approved for ^{212}Pb [27]. Patients expressing high levels of somatostatin receptor 2 (SSTR2) in neuroendocrine tumours will be subjected to treatment involving a peptide molecule labeled with ^{212}Pb ([^{212}Pb]VMT-Alpha-NET) for inoperable tumours affecting the lung, kidneys, head and neck, digestive tract, or adrenal glands (NCT06479811). Also, there is an ongoing clinical trial for unresectable and metastatic melanoma with [^{212}Pb]VMT01 that targets melanocortin sub-type 1 receptor (MC1R) (NCT05655312). The first-in-human clinical trial with ^{212}Pb labeled Pentixather is going to start for patients' treatment who have been diagnosed with and previously treated for atypical carcinoid lesions of the lung (NCT05557708). One safety study with a determined toxicity profile is completed for ^{212}Pb-TCMC-Trastuzumab in patients with HER-2 positive intraperitoneal cancers (NCT01384253).

Interest in ^{225}Ac is part of the coordinated research project (CRP, International Atomic Energy Agency, project No. F22075), which should provide data for the production process, quality control, and preclinical research for ^{225}Ac based radiopharmaceuticals, as well as recommendations with regard for infrastructure, training requirements, radiation protection, and waste management [28]. Currently, several ongoing clinical trials can be found on ClinicalTrials.gov using the search terms "actinium-225" and "Ac-225" [29]. Several mentioned trials with status recruiting are: phase 1 clinical study designed to investigate the safety, tolerability, dosimetry, biodistribution, and pharmacokinetics (PK) of [^{225}Ac]-FPI-2068 in adult patients with advanced solid tumours (NCT06147037); phase 1 dose-escalation study to evaluate the safety of ^{225}Ac–PSMA-617 in men with PSMA-positive prostate cancer (NCT04597411); phase I trial tests the safety, side effects, best dose, and effectiveness of ^{225}Ac-DOTA-Anti-CD38; a phase 1 study tests for the safety, side effects, and best dose of ^{225}Ac-DOTA-M5A in treating patients with CEA positive colorectal cancer (NCT05204147).

The first α-emitter radiopharmaceutical approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) is ^{223}Ra (Xofigo®), designed for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastatic disease. The international phase III clinical trial showed increased overall survival (15 months) after 6 cycles of ^{223}Ra dichloride injection while ensuring a favourable toxicity profile [30].

3. Astatine-211

The following paragraphs underline ^{211}At as an emerging α-emitting radioisotope for TAT. It was discovered in 1940 with atomic number 85 by Corson et al. at the University of California. The name astatine originates from the Greek word 'astatos', meaning 'unstable' [31].

The production is by irradiation of ^{209}Bi with a beam of α-particles accelerated to 28 MeV, following nuclear reaction ^{209}Bi(α,2n)^{211}At. After the irradiation, ^{211}At needs to be purified from the ^{209}Bi and traces of ^{211}Po [32]. Until now, two different processes for purification from the target are described: dry distillation and wet

extraction with acid treatment, with dry distillation being the preferred method and advantageous because of the minimal chemical exposure and less oxidation states [33], [34].

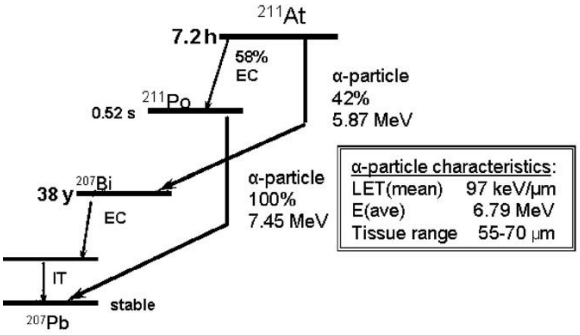

Figure 1. Decay scheme for ^{211}At and properties of ^{211}At α-particle [35]

It has favourable characteristics in terms of physical properties, production efficiency, and radiochemistry. Its half-life of 7.2 hours allows enough period to perform the steps of labeling the previously chosen vector, distribution and treatment, but still not enough for worldwide distribution. The decay path results with one α-particle per decay, with two different decay branches, until the formation of stable ^{207}Pb, as shown in the decay scheme in Figure 1 [35]. ^{211}At decay via electron capture to ^{211}Po producing polonium x-rays that permit counting the ^{211}At with conventional gamma-ray detectors, simplifying radiation dosimetry calculations [36].

The advantageous characteristics of ^{211}At make it a promising candidate for TAT, yet challenges remain in understanding and optimizing its chemical behaviour to develop reliable radiolabeling methods. It has a dual nature, exhibiting halogen and metal characteristics. ^{211}At has six different oxidation states (0, +I, +III, +V, +VII, and -I), allowing varying radiochemistry labeling strategies to be investigated and developed [37].

The preferred oxidation state of ^{211}At is -I, which is stable in a non-alkaline and reducing environments, such as sulphite or cysteine. ^{211}At (-I) exhibits characteristics that can be compared to those of iodine, its closest element, which allows it to form a carbon-astatine bond. However, this bond is weaker than the carbon-iodine bond [38], [39].

The carbon-astatine bond contributes to the in-vivo instability of ^{211}At radiopharmaceuticals. Numerous research groups are exploring strategies to overcome this issue through advanced precursor modifications, which involve introducing different substituents, employing aryl boronic esters, boron clusters, and other techniques [37], [40]. Recently, Hirata et al. showed that the in vivo stability of astatine could be significantly improved by introducing dimethyl carbamoyl neighbouring groups on astatobenzene compounds [41].

The strategies employed for ^{211}At labeling can be divided into electrophilic and nucleophilic approaches [42]. Electrophilic approaches include halo-deprotonation [43] and halo-demetallation reactions [44]. Nucleophilic approaches are halogen exchange [45], halo-dediazotation [12], aromatic nucleophilic substitution with iodonium salts [46] and copper mediated halo-deboronation [47].

Antibodies or their fragments are appropriate vectors to be labeled with ^{211}At because of the metallic properties and the isotope's similar half-life with the antibodies' kinetics [48]. The first approach for labeling antibody and F(ab)' fragment represents the two steps: electrophilic substitution with *N*-succinimidyl-astatobenzoate (SAB) as a precursor [49]. Then, the research group of CRCI²NA, to exceed the use of toxic tin precursor, used a two-step procedure but with a nucleophilic approach with aryliodonium salt as precursors [46]. For the same reason, Reilly et al. used a Cu-catalysed reaction with boronic ester precursors [47]. Furthermore, single-step strategies were developed, where firstly, the antibody is conjugated with prosthetic groups before labeling, thus saving time and improving radiochemical yields [50], [51].

Several ongoing clinical studies have been reported in the literature and on ClinicalTrials.gov, listed in Table 2 [52]. Osaka University Hospital in Japan is currently enrolling patients with differentiated thyroid cancer for a phase 1 clinical trial to evaluate the safety, pharmacokinetics, absorbed dose, and efficacy utilizing [^{211}At]NaAt. Also, they are recruiting patients for a phase 1 clinical trial to evaluate tolerability, safety, pharmacokinetics, absorbed dose, and efficacy using [^{211}At]PSMA-5, which targets prostate-specific membrane antigen in patients with castration-resistant prostate cancer. Additionally, a phase I clinical trial has been approved in Seattle, Washington, United States to use ^{211}At-OKT10-B10 before a donor stem cell transplant for the treatment of newly diagnosed, recurrent, or refractory high-risk multiple myeloma. In 2012, researchers from Sahlgrenska University Hospital (Gothenburg, Sweden) completed a dose-escalation study using ^{211}At MX35 F(ab')2 for intraperitoneal treatment of ovarian cancer. They published the safety, toxicity, and pharmacokinetic evaluation results and calculated the absorbed dose, leading them to the beginning of phase II study activities [53]. Besides this, three clinical studies using 211At-labeled radiopharmaceuticals have been completed: phase I, a dose-escalation study for the effectiveness of the radiolabeled monoclonal antibody 211At-ch81C6 for recurrent surgically resected glioblastoma at Duke University Medical Center (Durham, United States) and ^{211}At-labeled human serum albumin microspheres for recurrent carcinoma of the tongue at Carl Gustav Carus University Hospital (Dresden, East Germany) as a case study report of a palliative patient. [54]; and the first study on the uptake and accumulation of the radionuclide ^{211}At by the thyroid gland at the University of California Berkeley and San Francisco, United States [55].

4. NOAR-COST PROJECT

The Network for Optimized Astatine-labeled Radiopharmaceuticals (NOAR-COST project CA19114 https://astatine-net.eu/) is closely related to ^{211}At research, aimed to establish a European standard for treating specific types of cancer [56]. These include thyroid cancer, ovarian cancer, bladder cancer, glioma, and multiple myeloma. The project involves five working

Table 2. List of clinical studies with ^{211}At

NCT Number, Year started	Institution, Country	Study Title	Status	Study summary
NCT05275946 2021	Osaka University Hospital, Japan	Targeted Alpha Therapy Using Astatine (At-211) Against Differentiated Thyroid Cancer	Recruiting	Evaluation of safety, pharmacokinetics, absorbed dose, and efficacy, determination of the recommended dose for Phase II
NCT06441994 2024	Osaka University Hospital, Japan	Clinical Trial of Targeted Alpha Therapy Using [At-211]PSMA-5 for Prostate Cancer (Alpha-PS1)	Recruiting	Evaluation of tolerability, safety, pharmacokinetics, absorbed dose, and efficacy, determination of the recommended dose for Phase II
NCT04579523 2025	Fred Hutchinson Cancer Center, Washington, United States	^{211}At-OKT10-B10 and Fludarabine Alone or in Combination With Cyclophosphamide and Low-Dose TBI Before Donor Stem Cell Transplant for the Treatment of Newly Diagnosed, Recurrent, or Refractory High-Risk Multiple Myeloma	Not yet recruiting	Dose-escalation study
NCT04461457 2005	Sahlgrenska University Hospital, Sweden	Targeted Radiation Therapy for Ovarian Cancer: Intraperitoneal Treatment With 211-astatine-MX35 F(ab')2	Completed	Investigation of pharmacokinetics, safety, toxicity and dosimetry
NCT00003461 1998	Duke University Medical Center North Carolina, United States	Radiolabeled Monoclonal Antibody Therapy in Treating Patients With Primary or Metastatic Brain Tumors	Completed	Determination of the objective therapeutic response and toxicity of monoclonal antibody ^{211}At-ch81C6
/	Carl Gustav Carus University Hospital, East Germany	^{211}At-labeled human serum albumin microspheres for recurrent carcinoma of the tongue	Completed	Case report on one patient as a palliative care
/	University of California Berkeley and San Francisco, United States	^{211}At for thyroid gland disorder	Completed	Thyroid uptake and accumulation

groups dedicated to identifying vectors for different pathologies, improving radiochemistry, developing internationally harmonized protocols for radiation dosimetry in preclinical and clinical settings, exchanging knowledge, and creating an association of users comprising researchers and physicians.

The main production sites of ^{211}At in Europe, directly involved in this project, are the Copenhagen University Hospital (Copenhagen, Denmark) with the capability of producing a maximum of about 3.6 GBq of ^{211}At, Arronax (Nantes, France) with production up to ~1 GBq of ^{211}At [57], and no published data available from Forschungszentrum, Julich University (Julich, Germany). Recently, at the Radiation Centre POLATOM, located in Warsaw, Poland, a new cyclotron has been installed, and is expected to be actively involved in production and research for ^{211}At based radiopharmaceuticals. The Department of Medical Radiation Science within the University of Gothenburg (Gothenburg, Sweden) directly impacts this project by spreading knowledge for ^{211}At radiopharmaceuticals.

The World Astatine Community (WAC) was launched with representatives from the European Union, the Department of Energy (DOE) in the United States and the Japanese Atomic Energy Commission (JAEC) during this NOAR-COST project. Recently, China, South Korea, and South Africa joined the WAC [58]. The community aims to facilitate communication, share technology, and collaborate on global research to optimize and expand regional ^{211}At production networks internationally. This initiative is based on the primary idea of forming ^{211}At nodes to overcome limitations in the production and supply of this isotope.

5. Conclusion

Exploration and development of TAT using α-emitting radionuclides, such as ^{211}At, represent great promise for treating cancer. Favourable physical properties of ^{211}At make it an advantageous α-emitter for targeting micrometastases, residual cancer cells, and solid tumours while minimizing the damage to surrounding healthy tissues.

Significant advancements have been made in using ^{211}At. However, challenges persist, including improving the in-vivo stability of ^{211}At radiopharmaceuticals, the high cost associated with α-emitting radionuclides, and limited production capacities. Persistent research and clinical trials are essential to overcoming these barriers and fully realizing the potential of ^{211}At in cancer treatment. Continuous efforts are being made to expand the production of ^{211}At in Europe, the United States, and Japan, either by constructing new cyclotrons or using already existing accelerators' capabilities. Establishing a production site in the Balkan region could further enhance the potential benefits and feasibility of using ^{211}At. Distribution within a 500 - 700-kilometer radius would improve its accessibility and practicality for future applications.

The increasing international collaborations underscores the growing interest in improvement. The NOAR-COST project presents a global effort to integrate knowledge and development of ^{211}At and expand it through further research projects with closely associated aims.

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