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Development of PSMA-Targeted Alpha Therapy Using [^{211}At]PSMA-5

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Astatine (^{211}At) is an alpha-emitting nuclide with a 7.2-hour half-life that can be produced using a 30-MeV cyclotron. In recent years, the number of production sites worldwide has been increasing, attracting growing attention to ^{211}At. We have developed a novel ^{211}At-labeled PSMA-targeted agent ([^{211}At]PSMA-5). After conducting preclinical evaluations of its antitumor efficacy and safety, we initiated a first-in-human, investigator-initiated clinical trial in patients with metastatic castration-resistant prostate cancer. To date, the drug has been administered to a total of nine patients, and we have reported high accumulation of [^{211}At]PSMA-5 in recurrent and metastatic lesions. While further efforts are required for the social implementation of ^{211}At-based targeted alpha therapy, including the establishment of a supply chain and the accumulation of additional clinical evidence, PSMA-targeted alpha therapy using ^{211}At represents a promising treatment modality owing to its cyclotron-based production, sustainability, and clean decay characteristics.

Introduction

Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein that is highly expressed on the surface of prostate cancer cells.[1-3] While physiological expression is observed in certain normal tissues, including the salivary glands, kidneys, and small intestine, its expression is markedly upregulated in prostate cancer—particularly in advanced and metastatic castration-resistant prostate cancer (mCRPC)— and also correlates with tumor malignancy.

PSMA-targeted positron emission tomography (PET) using radiolabeled ligands (e.g., [^{68}Ga]Ga-PSMA-11, [^{18}F]PSMA-1007) has become a powerful tool for detecting recurrent and metastatic prostate cancer with high sensitivity and specificity. Furthermore, therapeutic applications have been developed using beta-emitters such as [^{177}Lu]PSMA-617 and alpha-emitters such as [^{225}Ac]PSMA-617. [^{177}Lu]PSMA-617 (Pluvicto®) has already been approved and is used for the treatment of mCRPC worldwide.[4-6] It has significantly extended overall survival in patients with mCRPC previously treated with androgen receptor pathway inhibitors (ARPI) and taxane therapy compared to the standard of care in the VISION trial.[7] Additionally, [^{177}Lu]PSMA-617 has been shown to prolong radiographic progression-free survival in taxane-naïve patients with mCRPC compared to ARPI switches, as reported in the PSMAfore trial.[8] However, some patients remain refractory or exhibit early recurrence after [^{177}Lu]PSMA-617 therapy. PSMA-targeted alpha therapy using ^{225}Ac or ^{212}Pb has been developed and evaluated in clinical trials.[9-17] However, the supply chain of these alpha emitters remains limited, particularly for ^{225}Ac, and poses a challenge for future global market distribution. Furthermore, there are also concerns about nephrotoxicity due to the redistribution of daughter nuclides.

Recently, there has been increasing interest in the cyclotron-produced alpha emitter, Astatine (^{211}At). It can be produced using a 30 MeV cyclotron bombarding a ^{4}He beam

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onto a natural bismuth (^{209}Bi) target.[18-22] As ^{209}Bi is abundant on earth, production of ^{211}At is scalable without depending on the import of raw materials, and a stable and sustainable supply can be achieved by establishing a cyclotron-based manufacturing base. Although the establishment of a supply chain network is essential for ^{211}At, as its physical half-life is 7.2 hours, the simple decay chain of ^{211}At offers advantages by eliminating the need for long-term radioactivity management and concerns related to the redistribution of daughter nuclides in the body.

Previous clinical applications of ^{211}At have been conducted via local administration, such as intracavity administration in brain tumor patients at Duke University with a ^{211}At-labeled ch81C6 antibody and intraperitoneal administration in Sweden for peritoneal dissemination of ovarian cancer using a ^{211}At-labeled MX35 F(ab')2 antibody.[23,24] Additionally, clinical trials using ^{211}At-labeled anti-CD38/CD45 antibodies in leukemia patients are being conducted at the Fred Hutchinson Cancer Center (Seattle, United States), although these have involved the somewhat unusual approach of marrow ablation prior to transplantation, and systemic administration for solid tumors has not yet been evaluated. At the University of Osaka in Japan, ^{211}At has been developed for systemic administration as a treatment of thyroid cancer, as it exhibits biodistribution patterns similar to iodine and accumulates via the sodium/iodide symporter. We have completed a first-in-human, investigator-initiated phase I trial evaluating a single intravenous administration of [^{211}At]NaAt in patients with ^{131}I-refractory thyroid cancer. We have confirmed that it can be safely administered, and some patients exhibited a $\geq$50% reduction in thyroglobulin levels along with decreased uptake on ^{131}I imaging, suggesting its therapeutic potential. An investigator-initiated clinical trial using [^{211}At]MABG is also being conducted at Fukushima Medical University, Japan.[25] Thus, the clinical application of astatine has been increasing in Japan in recent years.

Following [^{211}At]NaAt for thyroid cancer, we have also developed a novel ^{211}At-labeled PSMA-targeted compound ([^{211}At]PSMA-5) that demonstrated high tumor uptake and strong therapeutic efficacy in a mouse xenograft model of prostate cancer.[26] We have already started an investigator-initiated, first-in-human clinical trial for patients with mCRPC. In this review, we summarize the development of [^{211}At]PSMA-5 and its future landscape.

Production and Supply Chain of ^{211}At in Japan

^{211}At is produced via the nuclear reaction ^{209}Bi(α,2n)^{211}At by irradiating a bismuth target with alpha particles (Fig. 1). This requires a medium-energy cyclotron capable of accelerating alpha beams to an energy in the range of 28−29 MeV. In Japan, there are five facilities with cyclotrons capable of producing ^{211}At: the Research Center for Nuclear Physics (RCNP) of the University of Osaka, Fukushima Medical University, the RIKEN Nishina Center for Accelerator-Based Science, and the National Institutes for Quantum Science and Technology (QST) in Chiba and Gunma prefectures. Because of its short physical half-life of 7.2 hours, the supply of ^{211}At requires systematic coordination to enable timely distribution to universities and research institutions. Transportation can be conducted either in the form of solid ^{209}Bi targets irradiated with ^{4}He beams or as solutions obtained following chemical separation. To address these logistical challenges, a short-lived radionuclide supply platform was

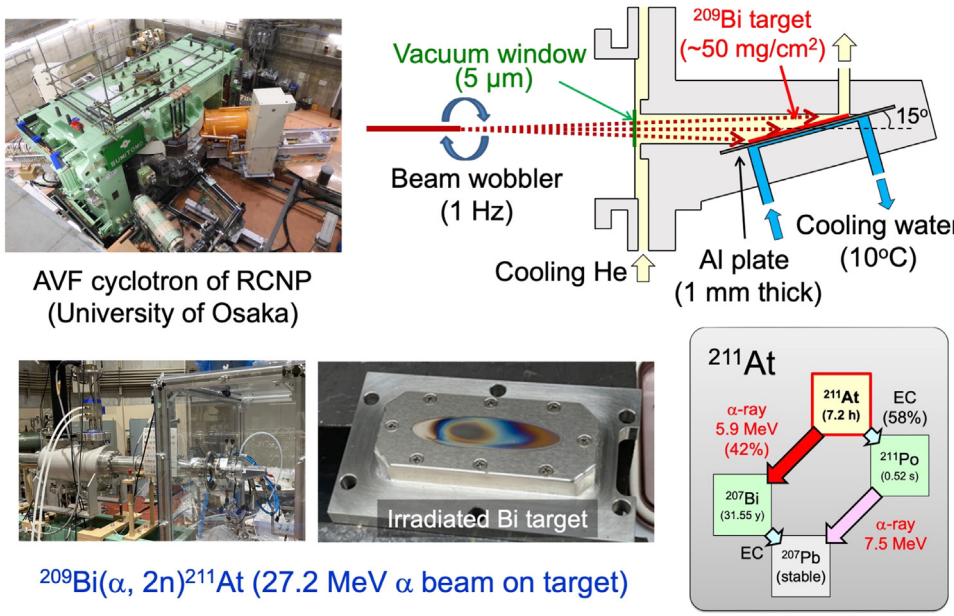

Figure 1 Production scheme of ^{211}At using AVF cyclotron at the research center for nuclear physics, the University Osaka, with a ^{209}Bi target irradiated by a 27.2 MeV alpha beam, and the decay scheme of ^{211}At.

established in Japan, and nationwide distribution of astatine has been continuously implemented since 2016. For clinical trials at the University of Osaka Hospital, ^{211}At is supplied from two primary sources: RIKEN and RCNP. At present, material is transported in the form of bismuth targets, which are subsequently processed into aqueous astatine solutions using an automated separation and purification system at the GMP-compliant investigational new drug manufacturing facility of the University of Osaka Hospital (Fig. 2). Although RIKEN is located approximately 500 km from the University of Osaka and transportation requires about seven hours, shipments have thus far been completed without any significant complications.

Radiosynthesis of [^{211}At] PSMA-5

^{211}At-labeled PSMA-5 was synthesized by the substitution reaction of ^{211}At with the dihydroxyboryl groups introduced into the corresponding precursor molecules, as described in a previous paper.[27] A representative labeling protocol consists of the addition of 0.03−0.30 mL of 0.1 mol/L potassium iodide, 0.03−0.70 mL of 7% sodium bicarbonate, an appropriate amount of aqueous ^{211}At, and purified water to 1−10 μg of precursor, with the total reaction volume adjusted to 0.1−1.0 mL. The mixture is then heated at 80-95 °C for 45 minutes. Following the reaction, the solution is purified using a solid-phase extraction cartridge to yield [^{211}At]PSMA-5.

The molecular structures of [^{211}At]PSMA-5 and other candidate compounds ([^{211}At]PSMA-1 and -6) are shown in Figure 3. The ^{211}At-labeled PSMA ligands were designed based on the molecular structure of PSMA-1007, which exhibits excellent pharmacokinetic properties and has already obtained marketing authorization in 13 European countries and Korea, with plans to expand worldwide, including Japan.[28] They are peptide-like molecules consisting of a pharmacophore (Glu-Ureido-Lys), a radionuclide labeling site (Aryl boronic acid), and a linker region. PSMA-1, -5, and -6 differ in the amino acid composition of their respective linkers, which are Gly-Lys, (R)-Glu-(R)-Glu, and Glu-Glu, respectively. To enhance metabolic stability, non-natural amino acid residues in the R-form were strategically incorporated into PSMA-5. This modification was intended to suppress enzymatic degradation by endogenous proteases following systemic administration. In contrast, the Gly-Lys motif introduced into the linker region of PSMA-1 was selected as a substrate for carboxypeptidase M, thereby promoting rapid renal clearance of the compound. Among the synthesized analogs, PSMA-6 retains the highest degree of structural similarity to PSMA-1007, thereby serving as a representative scaffold for comparative evaluation. PSMA-5 was identified as the lead development candidate from among the PSMA derivatives, following evaluation of the preclinical study results outlined below.

The radiochemical yields of [^{211}At]PSMA-5 were no less than 60% (radioactivity decay corrected), and the radiochemical purity of the products was greater than 96% SPE purification, both in preclinical studies and in the ongoing clinical trial.

Preclinical Evaluation of [^{211}At] PSMA-5: Efficacy

We performed preclinical evaluation using human prostate cancer cell lines with high expression of PSMA (LNCaP). We conducted comparative experiments between [^{211}At]PSMA-5 and [^{225}Ac]PSMA-617 using CCK-8 assay. LNCaP cell viability was assessed after exposure to increasing concentrations of [^{211}At]PSMA-5 or [^{225}Ac]PSMA-617 to compare their cytotoxic effects.[29] Viability data were evaluated by converting radioactivity concentration (kBq/L) into absorbed dose (Gy/mL) using the energy per decay (S-value). [^{211}At]PSMA-5 showed greater cytotoxicity than [^{225}Ac]PSMA-617 (Fig. 4 A).

Biodistribution was assessed using two methods: imaging and dissection with a gamma counter to measure the distribution in the body.[26] ^{211}At undergoes α-decay to its daughter nuclide polonium-211 (^{211}Po), and characteristic X-rays (76.9 and 79.3 keV) are emitted during this decay process. These X-rays fall within an energy range that can be detected

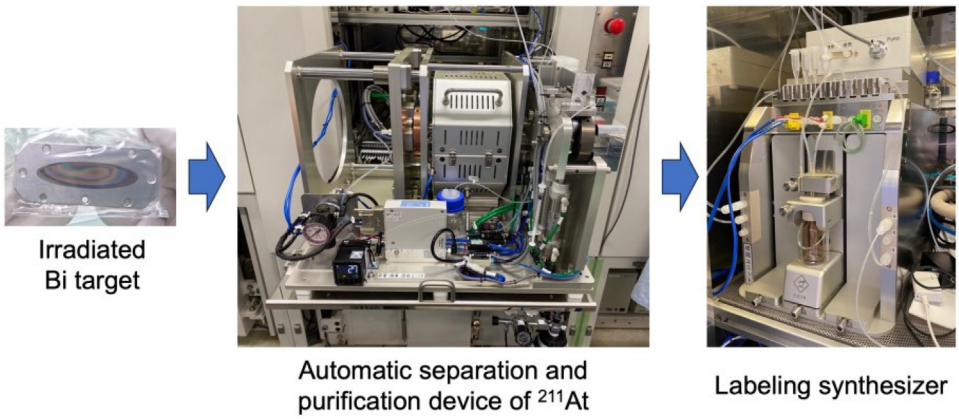

Figure 2 Automatic separation and purification of ^{211}At from a ^{209}Bi target, and subsequent labeling using a synthesizer.

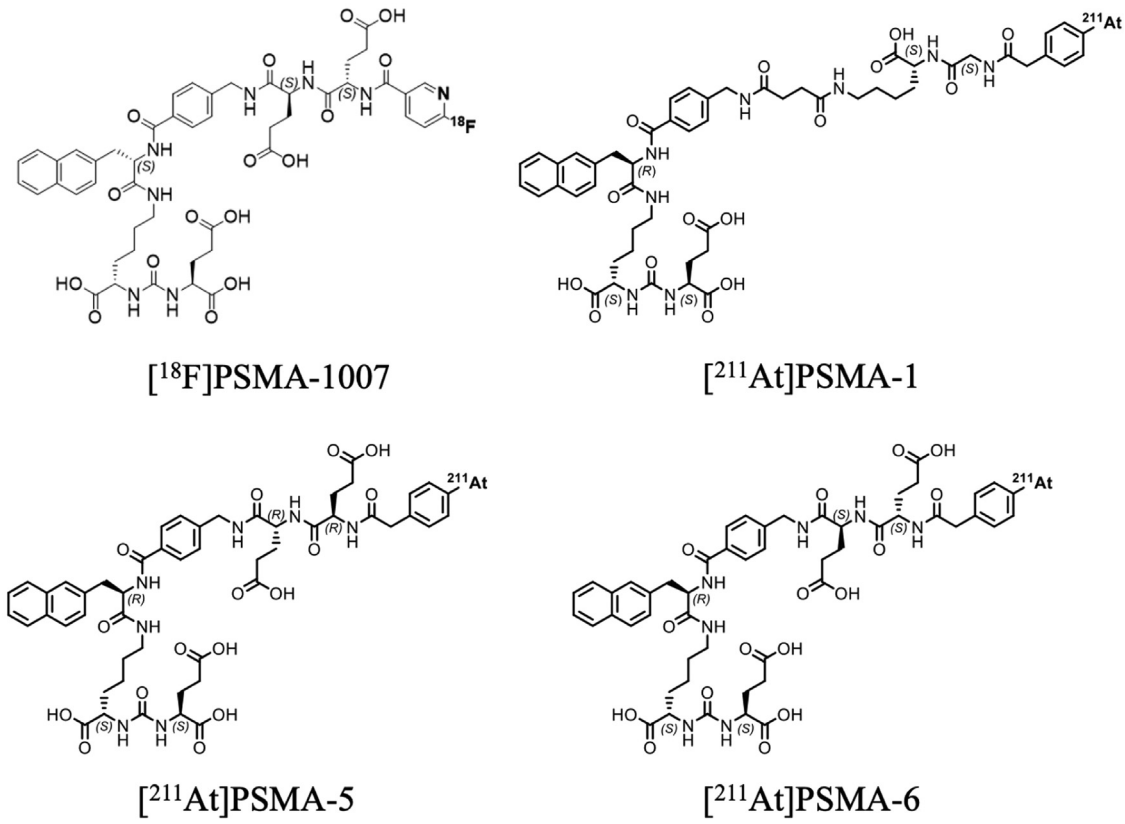

Figure 3 Molecular structures of [^{18}F]PSMA-1007, [^{211}At]PSMA-1, [^{211}At]PSMA-5, and [^{211}At]PSMA-6.

by gamma imaging cameras and enables single-photon emission computed tomography (SPECT) imaging. As a result, although ^{211}At itself is primarily an alpha-emitter, the accompanying X-ray emissions from its daughter ^{211}Po provide visualization of the in vivo distribution of ^{211}At-labeled radiopharmaceuticals, thereby supporting both dosimetry assessment and treatment monitoring in targeted alpha therapy. The planar images of [^{211}At]PSMA-5 are shown in Figure 4B. High uptake was observed in the tumor xenografts and kidneys at 3 and 24 h post-injection. In the kidneys, PSMA expression in the proximal tubules leads to physiological accumulation, and mice in particular often show high accumulation of PSMA-targeted drugs. Regarding tumor and kidney accumulation, the results of the dissection method are shown in Figure 4C. In comparison among [^{211}At]PSMA-1, [^{211}At]PSMA-5, and [^{211}At]PSMA-6, [^{211}At]PSMA-5 demonstrated the highest accumulation both at 3 and 24hrs post administration with increasing accumulating trend, whereas, kidney uptake was moderate with decreasing trend, which resulting in the highest in terms of tumor to kidney ratio among the three compounds.[26] Furthermore, [^{211}At]PSMA-5 showed higher therapeutic efficacy compared to [^{211}At]PSMA-1 without significant body weight loss (Fig. 4 D). Therefore, we selected [^{211}At]PSMA-5 for clinical translation.

In LNCaP cells, the IC_{50} value of [^{211}At]PSMA-5 was 0.32 nM when PSMA-617 was used as a blocking agent.[29] Following the intravenous administration of [^{211}At]PSMA-5, the compound exhibited a blood cell association rate of 29.3% and a plasma protein binding rate of 62.0% in mice. In cynomolgus monkeys, the respective values were 18.2% and 77.0%. Notably, [^{211}At]PSMA-5 remained chemically stable in the blood of both species, with no detectable radiolabeled metabolites observed in either plasma or urine samples, aside from trace amounts of free astatine (^{211}At) resulting from dehalogenation. These findings suggest that [^{211}At]PSMA-5 maintains high in vivo stability across rodent and non-human primate models, supporting its potential utility in targeted alpha therapy applications.

Preclinical Evaluation of [^{211}At]PSMA-5: Safety and Toxicity

After our decision to proceed with clinical translation, we had a consultation with PMDA (Pharmaceuticals and Medical Devices Agency), Japan's regulatory authority responsible for the scientific review of pharmaceuticals. As a result, the PMDA responded that if it was confirmed that there were no obvious safety issues in a single-dose general toxicity test, it would be possible to start the clinical trial. Subsequently, we conducted preclinical biodistribution and toxicity studies using [^{211}At]PSMA-5, which was administered to both normal male ICR mice (n=85) and cynomolgus monkeys (n=2).[30] We conducted biodistribution and toxicity evaluations to carefully initiate the first-in-human study, as species differences can occur with PSMA compounds (e.g., [^{18}F]PSMA-1007 was excreted in the urine in mice, but was barely excreted in humans). The SPECT images of a cynomolgus monkey after administration of [^{211}At]PSMA-5 are shown in Figure 5.

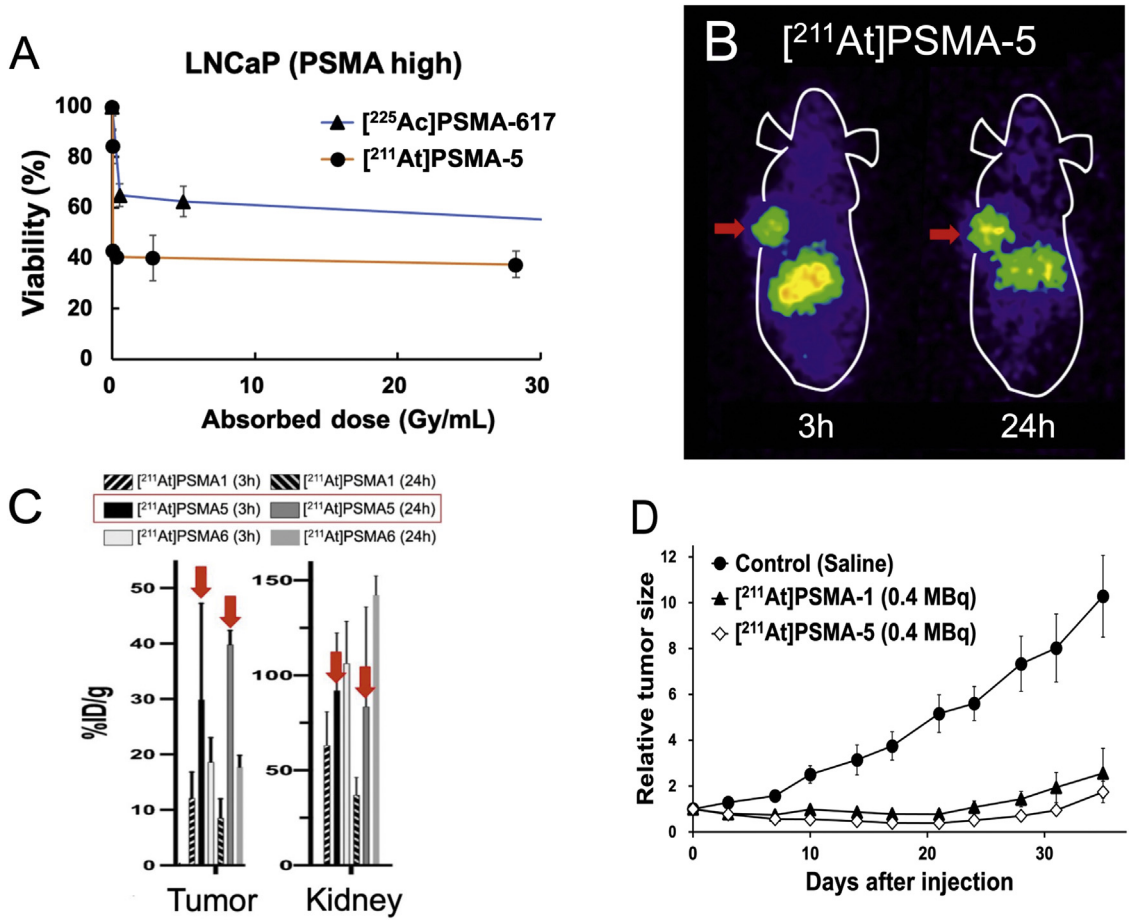

Figure 4 (A) Cell viability of LNCaP cells following treatment with [^{211}At]PSMA-5 or [^{225}Ac]PSMA-617. (B) Planar images of [^{211}At]PSMA5 in LNCaP xenograft mice. (C) Biodistribution of [^{211}At]PSMA-1, [^{211}At]PSMA-5, and [^{211}At]PSMA-6 in LNCaP xenograft model. (D) Tumor size in LNCaP xenograft mice after the single administration of [^{211}At]PSMA1 (0.4 MBq, n = 5), [^{211}At]PSMA5 (0.4 MBq, n = 12), or control (saline, n = 10).

The mice were divided into four groups for the toxicity study: 5 MBq/kg, 12 MBq/kg, 35 MBq/kg, and vehicle control, with follow-ups at 1 day (n=10 per group) and 14 days (n=5 per group). Monkeys were observed 24 hours post-administration of [^{211}At]PSMA-5 (9 MBq/kg). Blood tests and histopathological examinations were performed at the end of the observation period. Blood tests in mice indicated no significant myelosuppression or renal dysfunction, whereas the monkeys displayed mild leukopenia 24 hours post-administration. Despite the high accumulation in the kidneys and moderate uptake in the thyroid in the late phase, histological analysis revealed no abnormalities. Although some transient changes were observed in the salivary glands of mice and intestinal tracts of both mice and monkeys, such as dose-dependent single-cell necrosis/apoptosis, as well as a decrease in bone marrow cells in the 35 MBq/kg group of mice, no irreversible toxicity was observed in mice 14 days after administration.[30] This study identified no severe toxicities associated with [^{211}At]PSMA-5 (up to 35 MBq/kg), highlighting its novel and pivotal potential as a next-generation targeted alpha therapy for prostate cancer.

Clinical Evaluation of [^{211}At] PSMA-5

We also prepared an appropriate-use manual of [^{211}At]PSMA-5 which was approved by the Ministry of Health, Labour and Welfare[31] and conducted a second PMDA consultation regarding the starting dose and inclusion criteria for the clinical trial. Subsequently, we obtained the approval from the Institutional Review Board, submitted the clinical trial notification to PMDA, and commenced the first-in-human Phase I investigator-initiated clinical trial (NCT06441994) at the University of Osaka Hospital. It is designed to evaluate the safety, tolerability, pharmacokinetics, dosimetry, and preliminary efficacy of [^{211}At]PSMA-5 (PSW-1025). This trial represents the world's first clinical application of ^{211}At in prostate cancer and is expected to provide critical data for the development of PSMA-directed targeted alpha therapy. Recruitment began in May 2024, with a planned enrollment of 15 patients and study completion estimated in March 2027. Eligibility criteria include patients with mCRPC showing disease progression, defined by either a rising prostate-specific antigen (PSA) level or radiographic

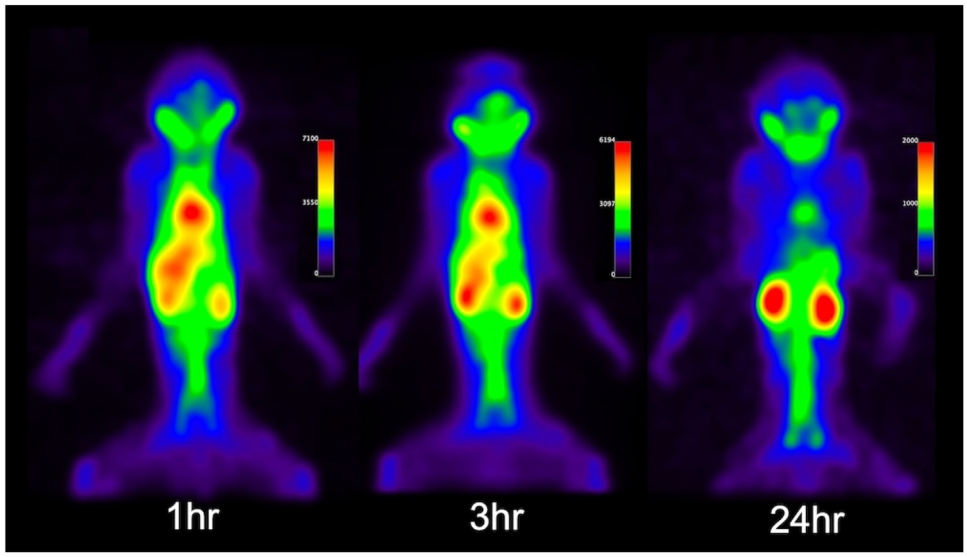

Figure 5 SPECT images (maximum intensity projection) of the monkey after administration of [^{211}At]PSMA-5 (9 MBq/kg).

progression. All patients must have previously received androgen receptor pathway inhibitors (enzalutamide, apalutamide) or a CYP17 inhibitor (abiraterone). Prior taxane-based chemotherapy is required unless patients are deemed ineligible. Key exclusions are recent systemic therapy within 4 weeks, radionuclide therapy (^{223}Ra or ^{177}Lu-PSMA-617) within 6 months, uncontrolled infections or comorbidities, and concurrent investigational drugs. The trial employs a dose-escalation scheme to determine the recommended Phase II dose. Patients are enrolled in sequential cohorts, with escalating doses of [^{211}At]PSMA-5 administered intravenously. Safety is closely monitored, and dose-limiting toxicities (DLTs) are assessed during the initial treatment cycles. Primary endpoints are safety and tolerability, including the incidence of DLTs and treatment-related adverse events. Secondary endpoints include pharmacokinetic measurements, biodistribution and dosimetry, and preliminary evidence of therapeutic efficacy. Efficacy is assessed by PSA response rates (≥50% decline from baseline), imaging-based evaluation using CT and RECIST criteria, and response on [^{18}F]PSMA-1007 PET. This clinical trial is expected to establish the feasibility of [^{211}At]PSMA-5 as a novel PSMA-targeted alpha therapy for patients with advanced-stage prostate cancer. The results will provide essential safety, dosimetry, and efficacy data to inform subsequent Phase II studies and accelerate the clinical development of radiopharmaceuticals using ^{211}At.

This study was funded by a Japanese government grant (AMED translational research grant, Seeds-F), initiated at the preclinical evaluation stage in 2022. In 2023, the project successfully passed the grant stage-gate with the highest evaluation, leading to the first-in-human administration just three years after the initial mouse experiment. This achievement was made possible not only by the experience gained from the earlier successful clinical translation of [^{211}At]NaAt, but also through close collaboration among the astatine production teams at the Research Center for Nuclear Physics and RIKEN, research collaborators at the Institute for Radiation Sciences, and the staff of the Departments of Medical Innovation and Nuclear Medicine at the University of Osaka Hospital—particularly Mr. Naka, Radiopharmacist of the Investigational New Drug Manufacturing Division.

The first-in-human SPECT/CT image of [^{211}At]PSMA-5 in a patient was already reported.[32] [^{211}At]PSMA-5 was administered to a patient with mCRPC refractory to standard treatment including androgen receptor signaling inhibitors, docetaxel, and cabazitaxel. SPECT/CT imaging was performed 3 hours post-administration using a VERITON-CT (Spectrum Dynamics Medical) equipped with a full-ring cadmium zinc telluride (CZT) detector, targeting the 79 keV X-rays from the daughter nuclide of ^{211}Po (Fig. 6). Both [^{18}F]PSMA-1007 PET/CT and [^{211}At]PSMA-5 SPECT/CT showed high accumulation in the local recurrence in the prostate area and in the left external iliac lymph node metastasis. Similar physiological accumulation was observed between the two modalities in the salivary glands, liver, spleen, small intestine, and kidneys without detectable urine excretion. Currently, we have reached the third dose level, with [^{211}At]PSMA-5 administered to a total of nine patients, and promising therapeutic effects are beginning to be observed in individuals with advanced mCRPC.

Future Landscape

Interest in ^{211}At is currently increasing worldwide, with new startup companies emerging in rapid succession and strong academic initiatives in several regions, such as NOAR Europe and Accelerate.EU. Alpha Fusion, a spin-out from the University of Osaka, is expanding rapidly, engaging in preclinical development, supply chain establishment, and preparations for upcoming clinical trials with [^{211}At]NaAt. Alpha Fusion has also initiated collaboration with Curadh to prepare for

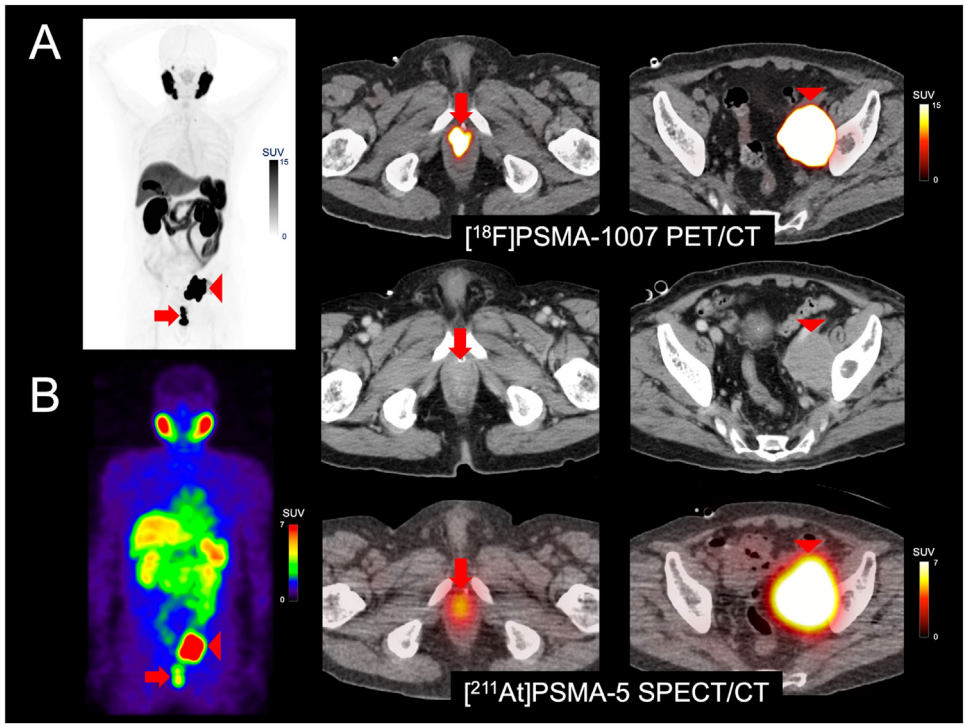

Figure 6 (A) [^{18}F]PSMA-1007 PET/CT and (B) [^{211}At]PSMA-5 SPECT/CT: maximum intensity projection (left) and fusion images (right). Contrast-enhanced CT images are shown in the middle. Both images showed high accumulation in the soft tissue mass in the prostate area (SUVmax=60.7 on [^{18}F]PSMA-1007 PET and 4.9 on [^{211}At]PSMA-5 SPECT) (arrows) and in the enlarged left external iliac lymph node metastasis (SUVmax=143.7 and 17.6, respectively) (arrow heads).

the launch of clinical trials in the United States. Nevertheless, in order to achieve the global spread of ^{211}At-based targeted alpha therapy, including [^{211}At]PSMA-5, the establishment of a robust international supply chain network is essential. In Europe, the number of supply bases of ^{211}At has expanded from two to six, and in the United States, companies such as Ionetix and NUSANO are preparing to commence production and distribution of this radionuclide.[33]

Regarding the collaboration between academia and industry, the World Astatine Community (WAC) and Japan Astatine Community (JAC) were established in 2023 as an international network of researchers, clinicians, and industry partners dedicated to advancing the production, preclinical evaluation, and clinical application of ^{211}At. Established to facilitate collaboration across disciplines and countries, the WAC and JAC serves as a global platform for sharing knowledge, harmonizing radiochemistry and radiobiology methodologies, and addressing key challenges in the clinical translation of ^{211}At-based radiopharmaceuticals.

Although clinical data on ^{211}At remain limited, clinical trials with [^{211}At]PSMA-5 are currently underway, and other ^{211}At-labeled PSMA-targeted compounds, such as [^{211}At]YF2 and [^{211}At]At-NpG-PSMA, are also being investigated or prepared for clinical evaluation.[34,35] PSMA-targeted alpha therapy using ^{211}At is expected to expand globally as a cyclotron-based, sustainable, and clean form of targeted alpha therapy, representing a promising next-generation theranostics.

Declaration of competing interest

TW, YS, KK, and AT; JC and FLG have patent applications for [^{211}At]PSMA-5 or [^{18}F]PSMA-1007, respectively. FLG is a scientific adviser to Alpha Fusion. The remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Tadashi Watabe: Formal analysis, Funding acquisition, Investigation, Methodology, Writing – original draft. **Sadahiro Naka:** Methodology, Writing – original draft. **Yoshifumi Shirakami:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Kazuko Kaneda:** Writing – review & editing. **Masashi Murakami:** Investigation, Methodology. **Atsushi Toyoshima:** Conceptualization, Investigation. **Jens Cardinale:** Conceptualization, Methodology. **Frederik L. Giesel:** Conceptualization, Supervision.

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