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Bringing Atom to Bedside with Targeted Alpha Therapy

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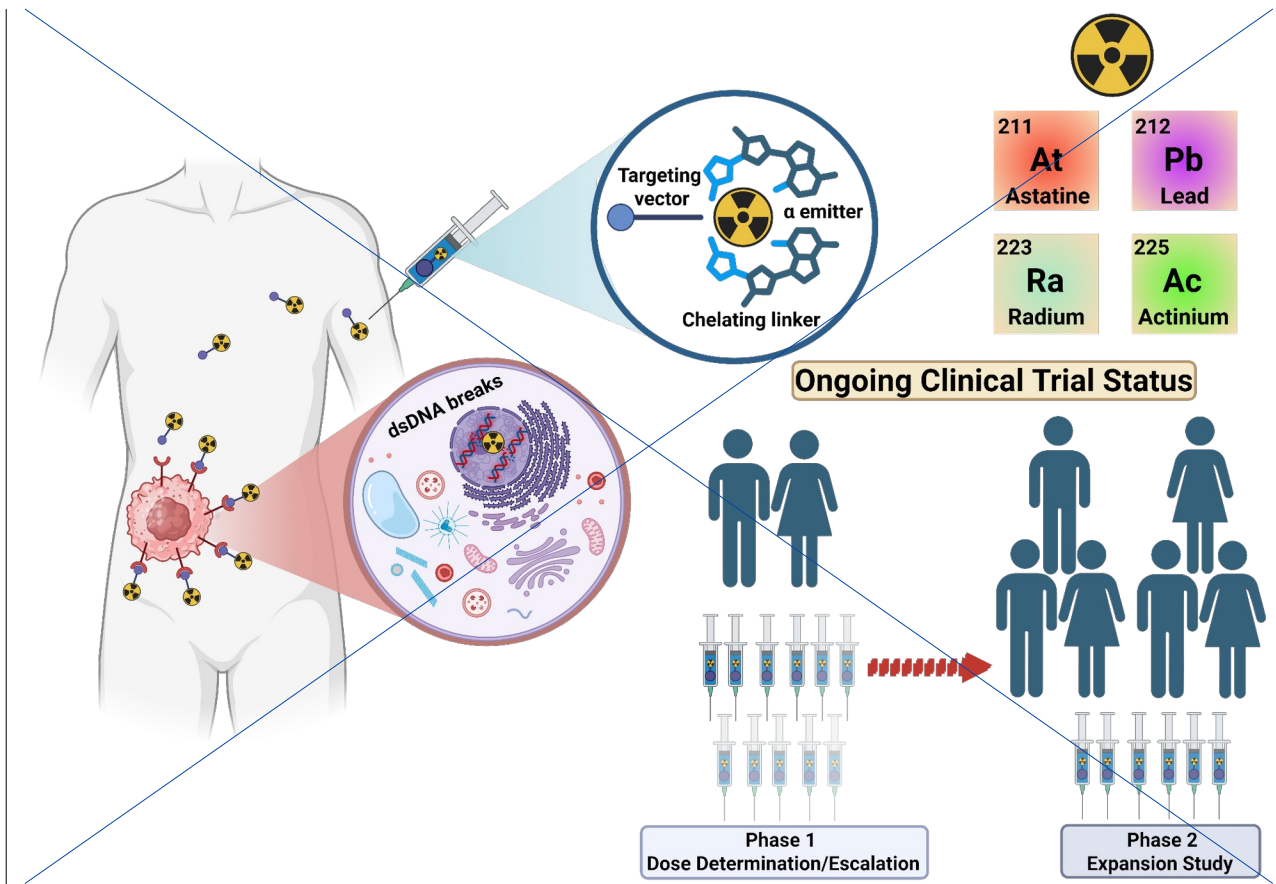
~~Targeted radionuclide therapy (TRT) is a hot topic in medicinal chemistry with targeted Targeted alpha therapy (TAT) is a growing field in medicinal chemistry garnering significant interest due~~owing to the ~~high linear energy transfer (LET) of~~ability of alpha particles, to selectively delivering radiation to tumor cells. ~~In the past year, these research efforts have Recent resulted in~~ clinical trials in TAT using ²²⁵Ac, ²¹²Pb, ²²³Ra, and ²¹¹At ~~as alpha emitters are highlighted herein.~~

Main Text

~~The field of Targeted radionuclide therapy (TRT) was pioneered with the establishment of~~began with the use of β^- emitting radionuclides as an alternative to conventional oncological treatments, such as chemotherapy and surgery. ~~This proved effective across a range of, for their therapeutic potential in a plethora of~~ malignant tumor cells.^{1,2} TRT ~~treatments consist of~~involves the ~~conjugation of~~ a targeting vector (a biomolecule targeting highly expressed receptors in specific tumor cells), a chelating or small molecule linker ~~to affix the radionuclide of interest~~for controlled release to the tumor site, and a radionuclide chosen ~~on the basis of~~based on its ~~mode of~~radioactive decay ~~modality~~(alpha, beta, or Auger emitters).

~~Although Alongside~~ β^- therapy, ~~targeted alpha therapy is the archetypal mode of TRT, the robust development in the field of (TAT) has shown promise in clinical trials owing to its stellar selectivity to treating~~ metastatic cancers and small tumors. ~~Owing to its. Moreover, the high linear energy transfer (LET) of α particles, which directs maximum radiation to a rather small area specifically targeting means you can hit~~ results in localized hits of several tumor cells, ~~in a small area whereas in contrast to in contrast to~~ β^- emissions, ~~which, which can~~ affect millions of cells over millimeter-scale range, ~~which can lead to potentially leading to with a higher possibility of~~ off-target damage to ~~surrounding neighboring~~ healthy cells. ~~TAT takes advantage of T~~these high energy α particles ~~to~~ thoroughly target tumor cells, leading to double-stranded breaks in DNA, ~~and which~~ minimizing the chances of recurrence. In the past year, there have been several promising clinical trials focused

on α -emitters, such as TAT with ^{225}Ac , ^{212}Pb , ^{223}Ra , and ^{211}At , handpicked for its biocompatibility, short half-lives, and high LET, which ~~are discussed~~ have been elucidated here (Fig. 1).



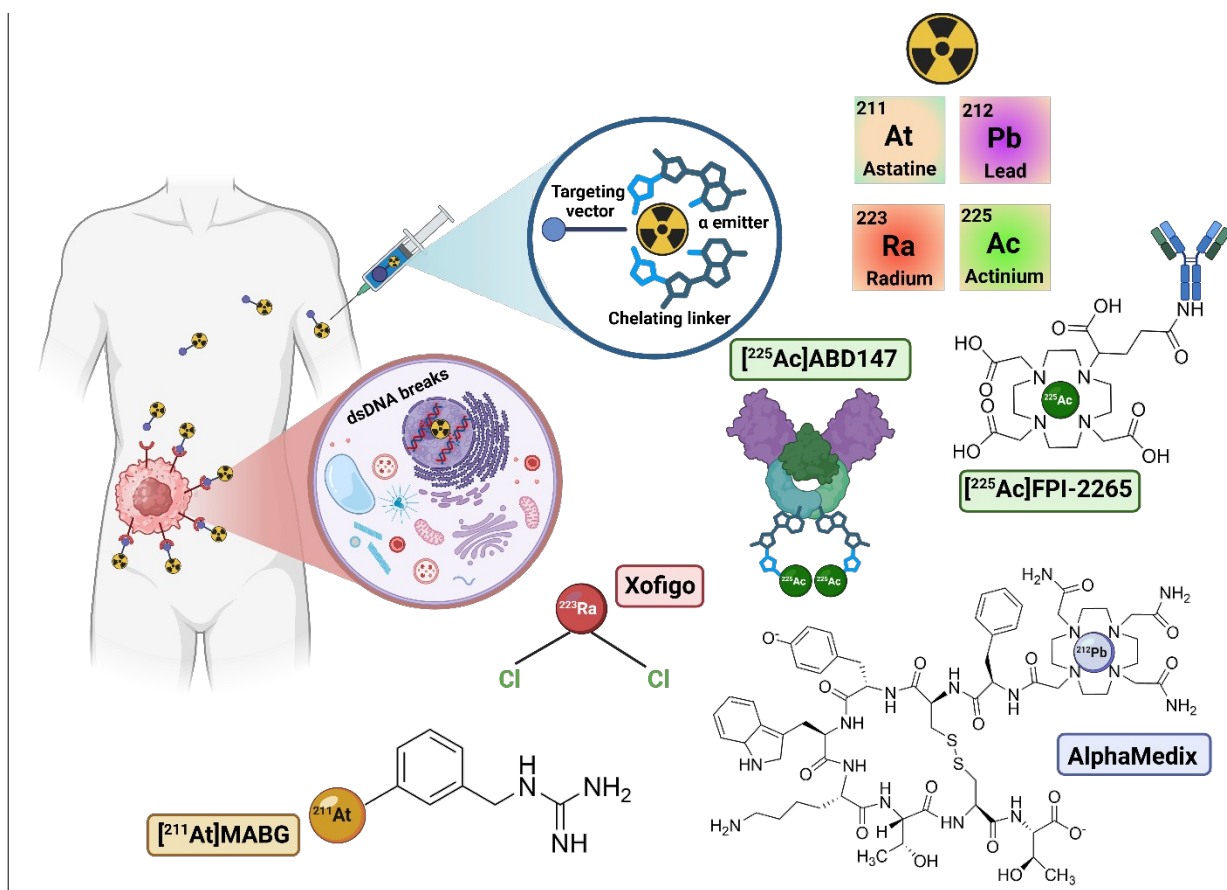


Fig. 1: Schematic representation of the administration of a radiopharmaceutical employed for the clinical trial of TAT. The radiopharmaceutical consists of an α emitter conjugated to a targeting vector (blue bubble). The α emitter (^{211}At , ^{212}Pb , ^{223}Ra , ^{225}Ac) induces cytotoxicity to tumors by causing double-stranded DNA breaks (red bubble). [Chemical structures of the drugs under clinical trial for TAT have been represented here](#)~~Clinical trials transition from phase 1 (dose determination/escalation) to phase 2 (expansion study).~~

^{225}Ac , with a half-life of 9.92 days and decay pathway ~~involving that releases~~ four α particles (~~with and~~ two β particles); ~~has been is~~ chelated ~~with linkers that allows the delivery of radioactivity as well as internal clearance from patients after desired therapeutic effect has been achieved~~ and bio-conjugated ~~with targeting vectors~~ ~~by exploiting various promising strategies to~~ selectively target primary and metastasized tumors. At pre-clinical stages, ^{225}Ac was investigated by Leamon's ~~group et al.~~ as a combination therapy with Olaparib (~~non-chemotherapy anti-cancer drug~~) to target prostate cancer in a mouse xenograft model.³⁻² They developed $[^{225}\text{Ac}]\text{FPI-2265}$, which involves the use of a prostate-specific membrane antigen (PSMA) binding ligand complexed to a ~~1,4,7,10-tetraazacyclododecane-1-glutaric acid-4,7,10-triacetic acid (DOTAGA)-based~~ chelating linker. ~~Although this compound~~ In combination with Olaparib, ~~this compound~~ demonstrated high efficiency in tumor growth decline ~~while also promoting and~~ lasting growth suppression, ~~as well as~~ $[^{225}\text{Ac}]\text{FPI-2265}$ ~~also showed providing a safe promising and therapeutic promise as a~~

monotherapy at a low dose of 1.23 MBq/kg with no ~~significant~~considerable toxicity at other dosages either. In 2025, Fusion Pharmaceuticals Inc. entered FPI-2265 and Olaparib combination therapy into clinical trials for patients with metastatic castration-resistant prostate cancer (mCRPC) (NCT06909825).

~~Led by Dr. Rudin, Aa group~~ Led by Dr. Rudin, in collaboration with Abdera (ABD) Therapeutics developed ABD147 ([²²⁵Ac]ABD147), which constitutes e~~coordinated~~²²⁵Ac -coordinated to a single variable domain on a heavy chain antibody (VHH-Fc) chelating linker ~~and this was conjugated the compound to the targeting vectorto target delta-like ligand 3 (DLL3) receptor ABD147 ([²²⁵Ac]ABD147).~~⁴³ This was developed to targets the delta-like ligand 3 (DLL3) receptor with high affinity (K_d of 2.8 nM), which is proteins are known to be highly elevated in many high-grade neuroendocrine tumors, such as large cell neuroendocrine carcinoma (LCNEC) as well as small cell lung cancer (SCLC). Upon binding, the drug internalizes ²²⁵Ac into DLL3 positive tumors ~~and, which then~~ emits α particles to cause double strand DNA breaks, thus inducing cytotoxicity. Pre-clinical investigations have demonstrated with [¹¹¹In]ABD147, a chemically analogous surrogate was found to ~~to~~ rapidly clears from normal tissues and preferentially accumulates in DLL3 positive tumors, while [²²⁵Ac]ABD147 showed robust anti-cancerous features along with enhanced survival in SCLC xenograft models.⁵ Currently, this is an open-label Phase 1a/b first in human study, where ~~in~~ Phase 1a focuses on dose-escalation to validate safety and tolerability, as well as pharmacokinetics and dosimetry for Phase 1b expansion, which will focus on preliminary drug efficacy (NCT06736418).

Apart from the use of a bioreceptor to target tumors, scientists have taken advantage of Radium's ability to mimic endogenous calcium in the treatment of mCRPC associated with bone metastases. By employing the α -emitting isotope, ²²³Ra with a half-life of 11.4 days and the tendency to accumulate in areas of high bone turnover, emits a localized dose to the nearby tumor cells. The FDA approved Xofigo ([²²³Ra]RaCl₂) is a first-in-class α -emitting pharmaceutical administered when testosterone-lowering treatments and surgeries are ineffective. Tombal and coworkers investigated the combinatorial effects of the testosterone blocker, Enzalutamide and Xofigo in patients with mCRPC, which demonstrated enhanced radiological progression-free survival (rPFS), however further investigation is required to confirm the overall enhancement to life.⁴
[Mention Clinical Trial ID]

One of the more exciting advancements in TAT is the use of radionuclides with short half-lives to enhance the therapeutic aspects of the radiation by discounting the detrimental flip side. ²¹²Pb is ~~another attractive an α particle-emitting radionuclide with a short half-life of 10.6 hours. The most common chelates for ²¹²Pb are DOTAM (TCMC) and DOTA.~~ Torgue et al. ~~and~~ coworkers demonstrated [²¹²Pb]Pb-DOTAMTATE (AlphaMedix), which combines 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic amide (DOTAM) with TATE, a somatostatin analog to targets somatostatin receptor 2 (SSTR2), which is known to be elevated in some neuroendocrine tumors (NETs). ~~to amalgamate the targeting features of somatostatin analog DOTAMTATE with anti-cancer cytotoxicity of ²¹²Pb.~~⁶⁻⁵ This analog targets somatostatin receptor 2 (SSTR2), which is known to be significantly elevated in some neuroendocrine tumors (NETs). This compound was compared with other octreotate and octreotide-based SSTR2 ligands. Pre-clinical investigations showed the compound to demonstrate high tumor retention due to initially have higher its robust pancreatic uptake as a result of its SSTR2

expression, however there was a more rapid clearing from the pancreas than the tumor, allowing for a longer tumor retention. This is currently in phase 2 of clinical trials for patients with positive somatostatin NET investigated in two groups: peptide receptor radionuclide therapy (PRRT) naïve or previous PRRT group (NCT05153772). More recently, ^{212}Pb is being clinically tried to target a wide range of SSTRs for, which could be on the surface of tumors located in head, in or near adrenal glands, lung, neck, kidney, and digestive tract (NCT06479811). Furthermore, AdvanCell Pty Limited developed [^{212}Pb]Pb-ADVC001 to target mCRPC, which is currently in phase 1b/2 dose escalation and expansion study, demonstrating the promise in the advancement of TAT (NCT05720130).

Finally, one of the most effective radionuclides employed in the clinical trials of TAT would have to be ^{211}At , an α emitter with a half-life of 7.2 hours and a simple decay scheme featuring one quantitative alpha-emission per decay, emitting one α -particle per decay. Additionally, due to it being a halogen, it shares chemical properties with iodine and can therefore be employed in similar ways, such as in the treatment of thyroid cancer. Capitalizing on this and the advantageous properties of alpha particles compared to the beta emissions used in radioiodine therapy, Watabe and coworkers at Osaka University investigated [^{211}At]NaAt as a treatment for refractory thyroid cancer. This study, which is currently in phase I clinical trial with and, which involves patients that were previously subjected to prior radioactive iodine therapy administered the astatinated conjugate, administered therapy are administered with [^{211}At]NaAt.⁶ The current dose escalation studies to extrapolate investigating dose-limiting toxicity and pharmacokinetics will impact future evaluation of its therapeutic efficacies. Along the lines of comparing halogen-based radionuclides,

Employing radionuclide therapy in the treatment of mCRPC has also been benefited by the development of ^{223}Ra , which is an α emitter with a half life of 11.4 days. Owing to its ability to mimic endogenous calcium, ^{223}Ra accumulates in areas of high bone turnover such as those in osteoblastic bone metastases, emitting a localized dose to the nearby tumor cells. While not targeted through a biological vector, the natural localization of ^{223}Ra has shown great applicability to mCRPC that has spread to the bones. The FDA approved Xofigo (^{223}Ra]RaCl₂) is a first-in-class α -emitting pharmaceutical administered when testosterone lowering treatments and surgeries are ineffective. The EORTC 1333/PEACE-3 trial investigated by Tombal and coworkers implements the combinatorial effects of enzalutamide, an androgen receptor inhibitor, and $^{223}\text{RaCl}$ injections in patients with mCRPC.⁷ It was found that this combination significantly improved radiological progression-free survival compared to either treatment administered individually. While further investigation following the secondary endpoint is needed to confirm improved overall survival, the results are promising. Additionally, advancements in monitoring ^{223}Ra treatment were made by Shegara et al. who assessed ^{68}Ga PSMA PET/CT imaging, verifying its ability to overcome the difficulties faced by other common imaging modalities and suggesting its use in future clinical trials.⁸

^{211}At , an α emitter with a half life of 7.2 hours, is an especially interesting candidate for alpha therapy due to its simple decay scheme, with 100% alpha emission and only one alpha particle emitted per decay. Additionally, due to it being a halogen, it shares chemical properties analogous to with iodine and can therefore be employed in similar ways, such as in the treatment of thyroid

cancer. Capitalizing on this similarity in thyroid accumulation, Watabe and coworkers at Osaka University investigated [^{211}At]NaAt as a treatment for refractory thyroid cancer in a phase I clinical trial.⁹ Patients who have previously undergone radioactive iodine therapy (RAI) were subjected to intravenously administration of [^{211}At]NaAt with dose escalation to evaluate dose-limiting toxicity and pharmacokinetics. These preliminary results will aid in the design of further clinical trials to assess therapeutic efficacy.

Meta-[^{131}I]iodobenzylguanidine ([^{131}I]MIBG), which is a β beta-emitter in radiopharmaceutical for the treatment of administered in metastatic pheochromocytoma and paraganglioma, that has shown limitations in efficacy increased adverse effects at the necessary dose for therapeutic efficiency. The alpha-emitting alternative, meta-[^{211}At]astatobenzylguanidine ([^{211}At]MABG), has the potential to overcome these limitations by utilizing the advantageous properties of alpha particles to minimize damage to surrounding healthy cells at a therapeutic dose while administering therapeutics dose. [What limitations?]. A team of scientists at Fukushima Medical University led by Dr. Zhao and Takahashi, in preparation of advancing this radiopharmaceutical to in-human clinical trial, conducted a single-dose toxicity study in mice over an extended period in preparation for in-human clinical trial.^{7,40} Statistical analysis of the data revealed an approximate lethal dose exceeding 80 MBq/kg, with no deterioration of the mice cohort up to this dose which resulted in overall deterioration of the mice's condition. [Good or bad? Did it kill the tumor or the mice itself?]. These results will inform the upcoming clinical trials led by the team, bringing ^{11}At one step closer to use in life-saving treatment.

Ultimately, current clinical trials on ^{225}Ac , ^{223}Ra , ^{212}Pb , and ^{211}At for TAT demonstrate a chronological advancement in terms of therapeutic efficacy in targeting tumors, biocompatibility in terms of patient survival, as well as employing isotopes of simpler decay scheme and shorter half-lives to diminish off-target effects. Advances in clinical trial phases will establish appropriate pharmacokinetics and dynamics to alleviate various oncological conditions with enhanced rPFS. Furthermore, current clinical and pre-clinical investigations conducted on a global scale demonstrates the ameliorating credence on TAT with avant-garde α -emitters, such as ^{149}Tb , ^{230}U , and ^{227}Th . [Please name more α -emitters] which are just beginning to step into the clinical limelight. The radiopharmaceutical toolbox is rapidly developing, with one of the most promising innovations being TAT. In 2025, there were plenty of advances in the field of TAT witnessed significant advancements, with several promising alpha-emitting radiopharmaceuticals employing ^{225}Ac , ^{212}Pb , ^{223}Ra , and ^{211}At , in preparation preparing for or advancing through clinical trials. Notable progress was seen with ^{225}Ac , ^{212}Pb , ^{223}Ra , and ^{211}At , with several formulations preparing for or entering phase I and phase II clinical trials. As these trials progress, and additional ones are brought online new potential therapeutics are developed, we can expect to see TAT will continue to evolve with improved treatment outcome, expansion to other cancer types, exploration of combination therapy, and advancements in dosimetry.

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Competing interests

The authors declare no competing interests.