

Bismuth-213

Subjects: [Medicine](#), [Research & Experimental](#)

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In contrast to external high energy photon or proton therapy, targeted radionuclide therapy (TRNT) is a systemic cancer treatment allowing targeted irradiation of a primary tumor and all its metastases, resulting in less collateral damage to normal tissues. The α -emitting radionuclide bismuth-213 (^{213}Bi) has interesting properties and can be considered as a magic bullet for TRNT.

bismuth-213

targeted radionuclide therapy

targeted alpha therapy

radiopharmaceutical

1. Introduction

In the diagnosis, monitoring, and treatment of cancer patients, nuclear medicine plays an important role. Radiopharmaceuticals consist generally out of three functional elements: (1) a vector molecule (or carrier) that shows high selectivity and affinity for a target; (2) a radionuclide; and (3) a linker or chelator to attach the former to the latter (Figure 1) [\[1\]\[2\]\[3\]\[4\]](#). A fundamental and critical component of a radiometal-based radiopharmaceutical is the chelator, the ligand that binds the radiometal ion in a stable coordination complex so that it can be properly directed to its molecular target in vivo [\[5\]\[6\]\[7\]](#). The radiopharmaceutical is mostly distributed within the body by the vascular system and allows targeting of a primary tumor and all its metastases. The specific decay characteristics of the radionuclide attached to the vector molecule determine if the radiopharmaceutical can be used for diagnostic (molecular imaging) or therapeutic (TRNT, targeted radionuclide therapy) purposes. The goal of targeted radionuclide therapy is to deliver sufficiently high doses of ionizing radiation to specific disease sites for cure, disease control, or symptomatic (e.g., pain of hormonal secretion) palliation. The biological effect of radionuclide therapy is obtained by three mechanisms: (1) Interaction of ionizing radiation with water in which chemically active free radicals (reactive oxygen species, ROS) are formed that can react with biomolecules (phospholipids, proteins, RNA, DNA, etc.), thereby irreversibly damaging the cells. (2) Direct interaction of ionizing radiation with DNA in which single-strand (SSB), double-strand (DSB), or cluster breaks can occur. (3) During treatment, a phenomenon called the abscopal effect can occur when radiation reduces not only the targeted tumor but also leads to the shrinkage of untreated tumors elsewhere in the body. Though the exact biological mechanisms accountable for the abscopal effect are yet to be identified, the immune system is considered the major player in this significant role [\[1\]\[8\]](#).

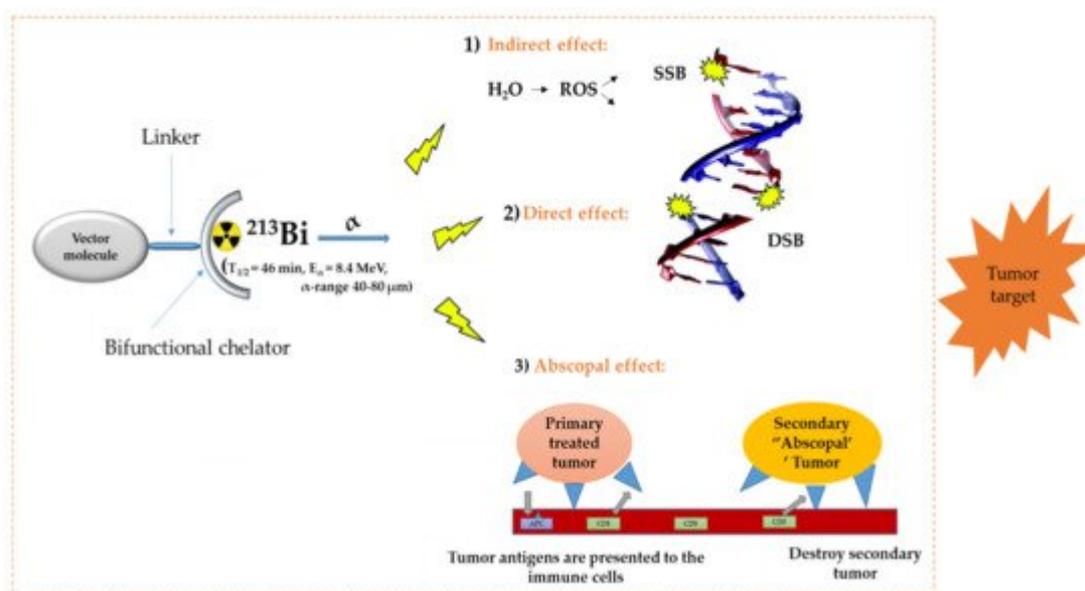


Figure 1. General concept of TRNT. ROS = reactive oxygen species, SSB = single strand break, DSB = double strand break, APC = antigen presenting cells, CD6 = cluster of differentiation 6. The DNA structure was reproduced from Gill and Vallis 2019, with permission from the Royal Society of Chemistry [9], Royal Society of Chemistry, 2019.

Auger-, beta minus (β^-), and alpha (α -) emitters are the three main subgroups of therapeutic radionuclides. α -decay is a radioactive decay in which an α -particle, consisting of two protons and two neutrons, is emitted from the nucleus. Tumor cells can be selectively destroyed, and the healthy tissue is minimally damaged due to the short penetration depth of α -particles (40–80 μm , corresponding to 2–10 cell diameter). An α -particle is characterized by a high-energy linear transfer (LET, 100 $\text{keV}/\mu\text{m}$) and thus a high relative biological effect (RBE). The high LET of α -particles results in a high rate of double-strand and cluster DNA breaks and consequently irreparable damage, producing the high kill rate of α -emitting radioisotopes both in normoxic as well as in a hypoxic tumor cell environment, which is known to be more resistant to photon and electron-based irradiation [10]. Therefore, targeted alpha therapy (TAT) can be considered as promising cancer treatment, especially suitable for the treatment of tumors with small diameters and which have a spatially homogeneous expression of the molecule targeted by the vector. Sufficient expression of the target in the malignant tissue must be confirmed before TAT can be initiated. This can be done by first performing a positron emission tomography (PET) or single photon emission computed tomography (SPECT) scan, after injection of the diagnostic sister of the therapeutic radiopharmaceutical. If the diagnostic radiopharmaceutical can truthfully predict the pharmacokinetics of its therapeutic sister, the diagnostic scan also allows accurate calculation of the dosimetry. This class of radiopharmaceuticals are called theranostic agents [11].

It is also important to mention here that the theranostic approach could also involve a single radionuclide agent—this theory stipulates the use of a single radionuclide, producing both therapeutic radiation and a low-energy γ -ray for SPECT to deliver dosimetric data. Examples of some of these radionuclides are ^{47}Sc ($T_{1/2} = 3.35 \text{ d}$) and ^{67}Cu ($T_{1/2} = 2.58 \text{ d}$) [12].

The α -emitting radionuclide ^{213}Bi ($T_{1/2} = 45.6$ min, $E_{\alpha} = 8.4$ MeV, $\gamma = 440$ keV, α -particle range = 40–80 μm) has interesting properties and might be considered as a magic bullet for TRNT [5][9]. However, like every cancer treatment modality, ^{213}Bi -based TAT has advantages and disadvantages. Indeed, ^{213}Bi can be considered as powerful precision ammunition, but it needs to be handled with care. In function of the target, the most suited vector molecule needs to be selected and the biological half-life of the vector should be compatible with the 45.6 min physical half-life of ^{213}Bi , which is substantially shorter than any therapeutic radionuclide in current routine clinical use. Further, an appropriate chelator needs to be carefully chosen to match the physical properties of ^{213}Bi .

2. Radionuclide Properties and Production of ^{225}Ac and Its Daughter ^{213}Bi

2.1. Decay Properties of ^{225}Ac and ^{213}Bi

^{225}Ac is the parent radionuclide of ^{213}Bi and is a relatively long-lived α -emitter with a half-life of 9.9 d. It decays via a cascade of six short-lived radionuclide daughters to stable ^{209}Bi with four net alpha particles emitted per decay (Figure 2). ^{213}Bi has a half-life of 45.6 min and shows branching decay (β^- and α decay), and most of the α -particles emitted originate from the β^- branch (see Figure 2). Indeed, it mostly decays via β^- emission to the short-lived α -emitter ^{213}Po ($T_{1/2} = 4.2$ μs , $E_{\alpha} = 8.375$ MeV, 97.8%, Figure 2). The residual 2.2% of ^{213}Bi decays leads to ^{209}Tl ($E_{\alpha} = 5.549$ MeV, 0.16%, $E_{\alpha} = 5.869$ MeV, 2.0%). Finally, ^{213}Po and ^{209}Tl decay via ^{209}Pb ($T_{1/2} = 3.25$ h, β^-) to stable ^{209}Bi [13].

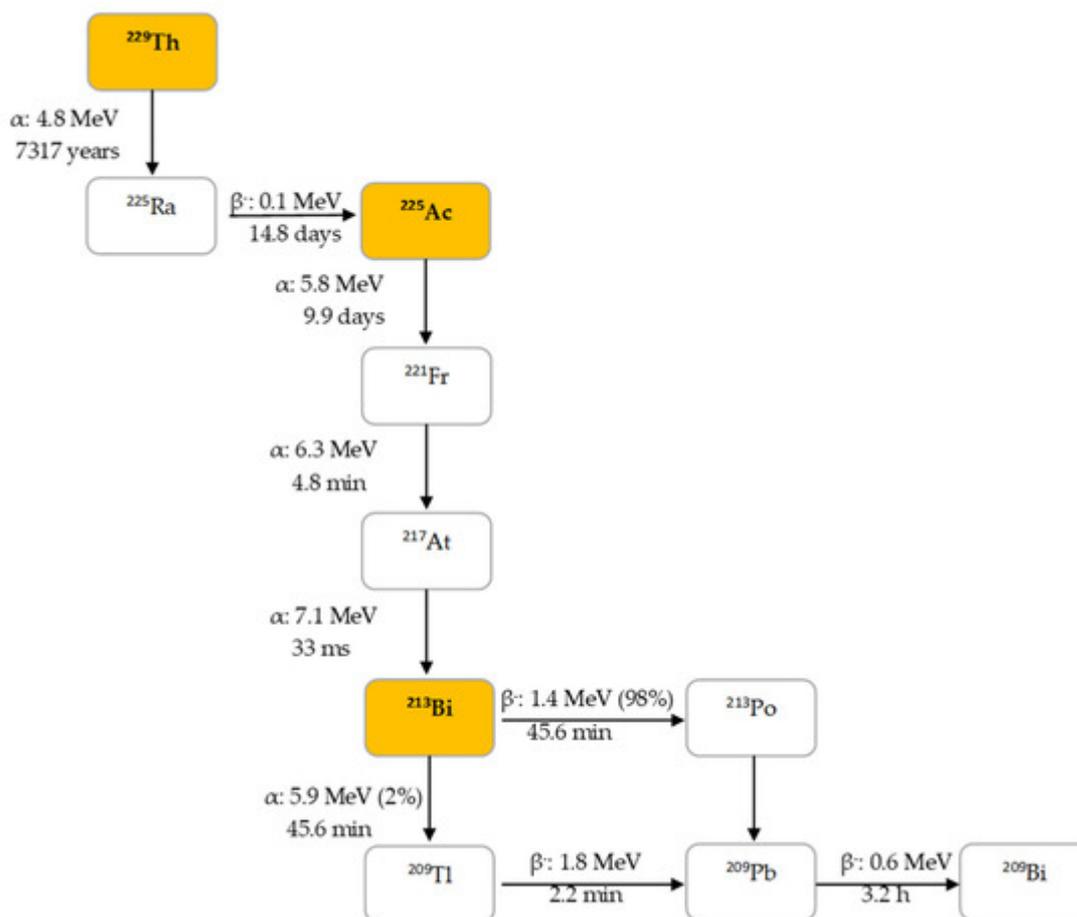


Figure 2. Decay chain of thorium-229 to ^{225}Ac and ^{213}Bi .

In human tissue, the α -particle released by ^{213}Po ($E_{\alpha} = 8.375$ MeV) has a path length of 85 μm . It is this radionuclide that produces >98% of the α -particle energy released per disintegration of ^{213}Bi and could be considered as the radionuclide that provides ^{213}Bi cytotoxicity. The bulk of the total particle energy released per disintegration of ^{213}Bi comes from α -decay, accounting for 92.7%, while 7.3% comes from β -particle emission, which includes the decay of ^{209}Pb [14]. The decay of ^{213}Bi is followed by the emission of a 435 keV-photon (98% abundance) that could potentially be used for SPECT with a gamma camera equipped with high energy collimators, permitting detailed evaluation of the biodistribution of ^{213}Bi in vivo [15].

It is noteworthy to mention that high activity $^{225}\text{Ac}/^{213}\text{Bi}$ generators are required to allow production of clinical amounts of ^{213}Bi . Optimal clinical injected activities depend on the vector molecules; for prostate-specific membrane antigen (PSMA)-targeting radiopharmaceuticals, this has been determined to be 4–8 MBq of ^{225}Ac [16] [17]. In contrast, to have the same number of alpha-particles emitted, 5–10 GBq is needed for ^{213}Bi -labeled radiopharmaceuticals [18]. This was estimated based on the Equations (1) and (2) below and the fact that ^{225}Ac delivers four α particles in its total decay scheme, while ^{213}Bi delivers net only one α particle. However, this is a rough estimation that does not consider the biological clearance of the radioprobes. Definitely, the much shorter half-life of ^{213}Bi compared to the half-life of ^{225}Ac is the key reason for the high activity levels that are needed when using ^{213}Bi for targeted radionuclide therapy (Equation (2)).

$$A = \lambda \cdot N \quad (1)$$

$$\lambda = \ln(2)/T_{1/2} \quad (2)$$

where A = activity (Bq, disintegrations per second), N = number of atoms, λ = decay constant.

2.2. Current Strategies for ^{225}Ac Production

Several approaches for ^{225}Ac and ^{213}Bi production have been recently reviewed and discussed in detail (Figure 3) [7][13]. The most utilized strategy is the radiochemical extraction of ^{225}Ac from ^{229}Th ($T_{1/2} = 7317$ years) sources originating from the decay of fissile ^{233}U . This results in “carrier free” ^{225}Ac using the generator method, but the available ^{233}U stocks and thus ^{229}Th stocks are limited because ^{233}U management is restricted by the requirements concerning non-proliferation of fissile materials. Most of the ^{213}Bi and ^{225}Ac used in clinical tests and research activities worldwide has so far been produced by this approach [19]. Two examples of ^{229}Th sources that can produce clinically relevant activities of ^{225}Ac are (1) the US Department of Energy, Oak Ridge National Laboratory (ORNL) in Oak Ridge, TN, United States of America and (2) the Directorate for Nuclear Safety and Security of the JRC of the European Commission in Karlsruhe, Germany. Additionally, at the Belgian Nuclear Research Centre (SCK CEN) in Mol, Belgium, very pure sources of ^{229}Th were identified, processed, and used for pre-clinical studies [20]. The total global annual ^{225}Ac production volume is approximately 55–65 GBq [21] and cannot meet the growing demand for ^{225}Ac , but interestingly, it has been reported that stocks will increase by extraction of additional ^{229}Th from US legacy wastes [7].

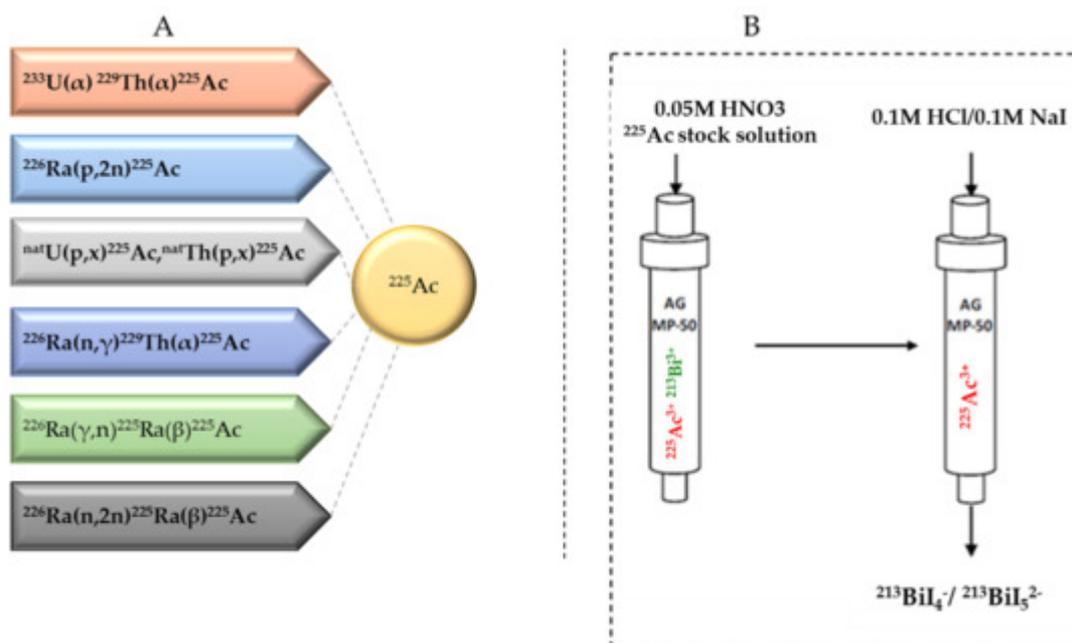


Figure 3. (A) Production routes for ^{225}Ac and (B) the $^{225}\text{Ac}/^{213}\text{Bi}$ generator.

Cyclotron production is an alternative method for ^{225}Ac production. Medium-energy proton irradiation of ^{226}Ra using the reaction $^{226}\text{Ra}(p,2n)^{225}\text{Ac}$ is considered to be a viable approach. The advantage of this method is the

widespread availability of appropriate cyclotrons worldwide, especially in Europe [22][23], and high amounts of clinical doses of ^{225}Ac could be produced in a reliable way. It is important to mention that medical cyclotrons used to produce radioisotopes (15–25 MeV) are considered to be feasible for basic and applied research [24]. The downside with this approach is that ^{226}Ra is not an easy isotope to work with due to the presence of the highly radiotoxic noble gas ^{222}Rn in its decay chain. Therefore, it is unlikely that this will ever enter a clinical cyclotron.

Further, high-energy proton irradiation (0.6–2 GeV) of uranium and thorium spallation targets via the reaction $^{\text{nat}}\text{U}(\text{p},\text{x})^{225}\text{Ac}$ is another approach for the production of ^{225}Ac . The existence of several suitable high-energy proton facilities makes this an achievable prospect. However, such accelerator-produced ^{225}Ac contains a low percentage (0.1–0.3%) ^{227}Ac ($T_{1/2} = 21.77\text{y}$) at the end of bombardment, which might be a serious limitation in terms of clinical translation and waste management [25][26]. Nevertheless, ^{225}Ac obtained through high-energy accelerators could be entirely appropriate for $^{225}\text{Ac}/^{213}\text{Bi}$ generator production (see 2.3), even with co-production of ^{227}Ac , as all actinium species will be retained on the generator.

Another production path being explored is transmutation of ^{226}Ra to ^{229}Th by an intense neutron flux. This will lead to three successive neutron capture reactions: $^{226}\text{Ra}(\text{n},\gamma)^{227}\text{Ra}$, $^{227}\text{Ac}(\text{n},\gamma)^{228}\text{Ac}$, and $^{228}\text{Th}(\text{n},\gamma)^{229}\text{Th}$. However, production of many orders of magnitude of ^{228}Th ($T_{1/2} = 1.9\text{ y}$) intermediate, and handling of the radium target remains a challenge [18].

$^{226}\text{Ra}(\gamma,\text{n})^{225}\text{Ra}$ is another reaction path for ^{225}Ac production that has been determined experimentally [27][28]. This strategy explored irradiation of old radium needles with high-energy X-rays from electron linear accelerators (linacs).

Finally, transmutation of ^{226}Ra to ^{225}Ra by fast neutrons via the reaction $^{226}\text{Ra}(\text{n},2\text{n})^{225}\text{Ra}$ is also under consideration. It is noteworthy to point out that the limitation for all the strategies discussed is the handling of the radium targets. However, earlier results with these methods have been promising [22].

To conclude, all clinical studies with $^{225}\text{Ac}/^{213}\text{Bi}$ radiopharmaceuticals were performed to date with ^{225}Ac originating from ^{229}Th stocks, but other accelerator-based production routes were heavily investigated in the last decade. This progress will hopefully assure reliable production and delivery of ^{225}Ac to radiopharmacy institutes in the near future, allowing more preclinical research and multicenter clinical trials with both ^{225}Ac and ^{213}Bi -radiopharmaceuticals.

2.3. $^{225}\text{Ac}/^{213}\text{Bi}$ Radionuclide Generators

^{225}Ac can be loaded on $^{225}\text{Ac}/^{213}\text{Bi}$ generators to deliver ^{213}Bi on site, but it can also be used directly as a therapeutic radionuclide. $^{225}\text{Ac}/^{213}\text{Bi}$ generators are well explored and discussed [29][30][31]. The most established strategy is based on the direct generator method, in which the parent ^{225}Ac in acidic solution (e.g., 0.05M HNO_3) is strongly retained by the sorbent (e.g., AG MP-50 cation exchange resin) and ^{213}Bi is eluted. Elution is performed generally with a mixture of 0.1M $\text{HCl}/0.1\text{M}$ NaI to obtain ^{213}Bi in the form of $^{213}\text{BiI}_4^-$ and $^{213}\text{BiI}_5^{2-}$ that can be directly used for radiochemistry purposes. (Figure 3) [7]. These generators can potentially be used clinically due to the

relatively long parent half-life, which allows shipment of the generator to radiopharmacy facilities at long distance. Additionally, the transient equilibrium of the ^{225}Ac - ^{213}Bi permits elution at approximately every 3 h [32]. These generators can provide weeks of reliable in-house generation of ^{213}Bi for radiolabeling purposes [33]. High activity (up to 4 GBq ^{225}Ac) generator systems, developed at JRC Karlsruhe, have been reported with yields of ^{213}Bi elution exceeding 80% and low breakthrough of ^{225}Ac of less than 0.2 ppm [32].

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