

# Eight Promising Radionuclides for TAT

Subjects: Pharmacology & Pharmacy

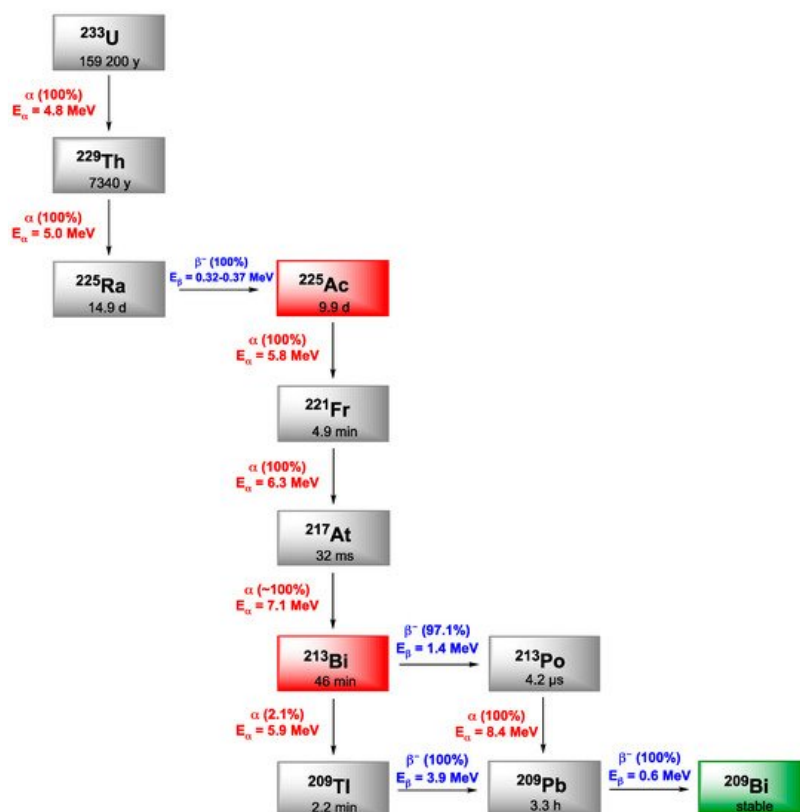
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Among all existing radionuclides, only a few are of interest for therapeutic applications and more specifically for targeted alpha therapy (TAT). Actinium-225, astatine-211, bismuth-212, bismuth-213, lead-212, radium-223, terbium-149 and thorium-227 are considered as the most suitable. Despite common general features, they all have their own physical characteristics that make them singular and so promising for TAT. These radionuclides were largely studied over the last two decades, leading to a better knowledge of their production process and chemical behavior, allowing for an increasing number of biological evaluations. The aim of this review is to summarize the main properties of these eight chosen radionuclides. An overview from their availability to the resulting clinical studies, by way of chemical design and preclinical studies is discussed.

Keywords: targeted alpha therapy ;  $\alpha$ -emitters ; actinium-225 ; astatine-211 ; bismuth-212 ; bismuth-213 ; lead-212 ; radium-223 ; terbium-149 ; thorium-227

## 1. Actinium-225

Actinium is the first element of the actinide series, and among its 32 known isotopes, only  $^{228}\text{Ac}$  and  $^{227}\text{Ac}$  occur naturally as part of the decay chains of  $^{232}\text{Th}$  and  $^{235}\text{U}$ , respectively.  $^{227}\text{Ac}$  is the most abundant isotope, exhibiting a long half-life of 21.7 years and decaying mainly through  $\beta^-$  emissions.  $^{228}\text{Ac}$  is also a  $\beta^-$  emitter and is extremely rare.  $^{225}\text{Ac}$  is part of the  $^{237}\text{Np}$  decay chain which has disappeared in Nature but was recreated artificially.  $^{225}\text{Ac}$  exhibits features that have made it a promising candidate in nuclear medicine applications. It has a half-life of 9.9 days. Its disintegration follows a six-step decay chain to reach stable nuclei, that generates multiple alpha particles contributing to increasing its potential cytotoxicity in comparison with other  $\alpha$ -emitters (Figure 1). Besides, with the  $\gamma$ -emission of some of its daughter nuclides such as  $^{221}\text{Fr}$  or  $^{213}\text{Bi}$ , it provides the possibility to trace it after injection. Nevertheless, it has to be mentioned that these radiations make the reaction monitoring difficult and the secular equilibrium has to be reached before one can measure a reliable radiochemical yield (at least 6 h).



## 2. Astatine-211

Astatine is often reported as the rarest natural element on Earth, and exhibits 32 isotopes, none of them being stable. Even if most of these isotopes are  $\alpha$ -emitters, only  $^{211}\text{At}$  exhibits suitable physical properties for TRT. It decays with a half-life of 7.21 h and following a dual branch process resulting in the emission of 5.9 and 7.5 MeV  $\alpha$  particles as well as X-rays (77–92 keV). Whatever the branch, one alpha particle is emitted, qualifying  $^{211}\text{At}$  as a 100%  $\alpha$ -emitter. It is interesting to notice that potential radiotoxicity of  $^{211}\text{At}$  daughters' is negligible; especially because of the short half-life of  $^{211}\text{Po}$  and the very low amount of  $^{207}\text{Bi}$  generated. Finally, the emission of X-rays in the adapted energy range of common  $\gamma$ -detectors, offers the possibility of monitoring by single photon emission computed tomography (SPECT) imaging (Figure 3).

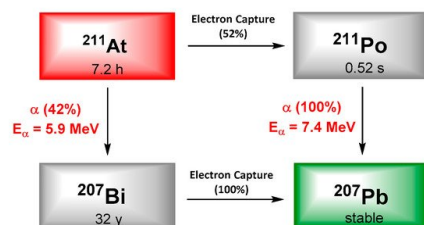


Figure 3. Simplified decay scheme of  $^{211}\text{At}$ .

## 3. Bismuth-213

Bismuth belongs to group 15 of periodic classification and exhibits 35 isotopes, most of them having short half-lives (from ns to a few minutes) and only one is considered stable,  $^{209}\text{Bi}$ , due to a very long half-life of  $1.9 \times 10^{19}$  years. Among all these isotopes, only  $^{212}\text{Bi}$  and  $^{213}\text{Bi}$  have demonstrated promising features for investigation in targeted alpha therapy.

$^{213}\text{Bi}$ , a daughter isotope of  $^{225}\text{Ac}$ , decays by  $\alpha$  (2.2%) and  $\beta^-$  (97.8%) emission with a half-life of 46 min. It decays to the stable  $^{209}\text{Bi}$  via successive decays resulting in  $\beta^-$  emissions (0.6–2 MeV) and the emission of one  $\alpha$  particle (5.9–8.4 MeV). The total emitted energy of  $^{213}\text{Bi}$  can be attributed at 90% to  $\alpha$ -particles and can explain its more pronounced cytotoxicity. In addition, the emission of gamma rays with an energy of 440 keV offers the possibility of imaging by SPECT (Figure 1).

## 4. Bismuth-212

$^{212}\text{Bi}$  arises from the decay sequence of  $^{228}\text{Th}$  (1.9 y) and results in  $^{208}\text{Tl}$  (3.1 min) via 36% of  $\alpha$ -emission and by 64% to  $^{212}\text{Po}$  (0.3  $\mu\text{s}$ ) after  $\beta^-$ -emission, both daughters leading to stable  $^{208}\text{Pb}$ .  $^{208}\text{Tl}$  decay occurs through high energy  $\gamma$ -emission (2.6 MeV), which necessitates adapted protection for all the handling phases. Like  $^{213}\text{Bi}$ ,  $^{212}\text{Bi}$  exhibits a short half-life (60.6 min) which requires rapid targeting as well as efficient production of radiolabeled carrier molecules. On the other hand, in vivo release issues regarding  $^{212}\text{Bi}$  daughter radionuclides are negligible due to the short decay chain of  $^{212}\text{Bi}$  to stable  $^{209}\text{Bi}$  and the short half-lives of the daughters induced (Figure 6).

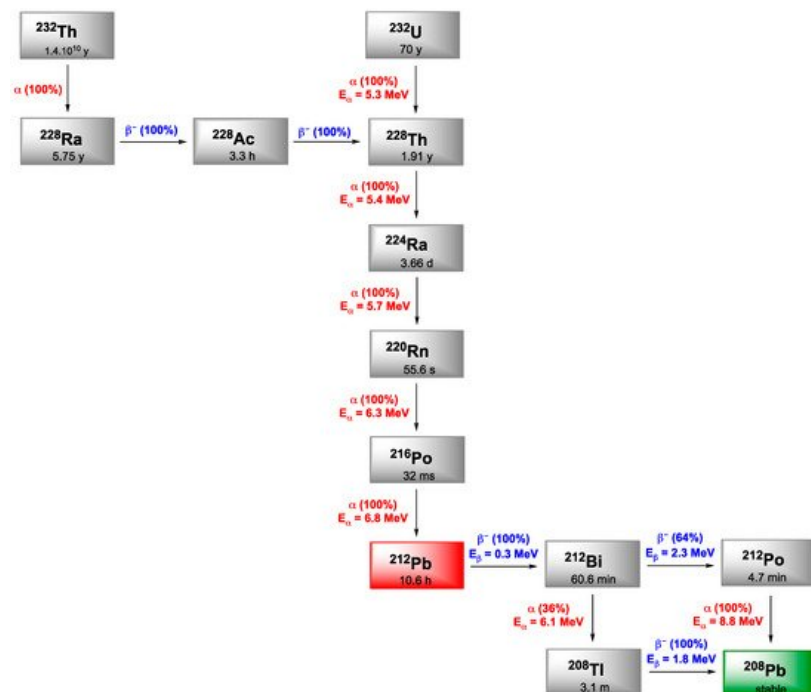


Figure 6. Decay schemes for the production of  $^{212}\text{Bi}$  and  $^{212}\text{Pb}$ .

## 5. Lead-212

Lead is often presented as the heaviest stable element in the periodic classification and exhibits four stable isotopes:  $^{204}\text{Pb}$ ,  $^{206}\text{Pb}$ ,  $^{207}\text{Pb}$  and  $^{208}\text{Pb}$ . Among its 38 reported isotopes, five would have appropriate properties for detection ( $^{203}\text{Pb}$ ,  $^{210}\text{Pb}$ ,  $^{211}\text{Pb}$ ,  $^{212}\text{Pb}$ ,  $^{214}\text{Pb}$ ) but only two are suitable for clinical application, in imaging with  $^{203}\text{Pb}$  (SPECT) and therapy with  $^{212}\text{Pb}$ .  $^{212}\text{Pb}$  is a  $\beta^-$ -emitter but its interest in TAT comes from the fact that its first daughter is  $^{212}\text{Bi}$  (Figure 6). The short half-life of  $^{212}\text{Bi}$  can be overcome by using  $^{212}\text{Pb}$  in vivo generator of  $^{212}\text{Bi}$ .

## 6. Radium-223

Radium is an alkaline earth metal originating from the decay process of  $^{235}\text{U}$ ,  $^{238}\text{U}$  or  $^{232}\text{Th}$ . Among its 33 known isotopes, only four occur naturally:  $^{228}\text{Ra}$  (5.75 y) and  $^{224}\text{Ra}$  (3.63 d) from  $^{232}\text{Th}$ ,  $^{226}\text{Ra}$  (1600 y) the most abundant, from  $^{238}\text{U}$  (stable) and  $^{223}\text{Ra}$  (11.4 d) from  $^{235}\text{U}$  (703,800,000 y).  $^{223}\text{Ra}$  and  $^{224}\text{Ra}$  are both  $\alpha$ -emitters but the decay chain of  $^{224}\text{Ra}$  includes daughter nuclides such as  $^{220}\text{Rn}$  (56 s) and  $^{212}\text{Pb}$  (10.6 h) with non-negligible half-lives that could be problematic because of their potential redistribution in the whole organism. Therefore,  $^{224}\text{Ra}$  has been much less investigated than  $^{223}\text{Ra}$ , mainly for treatment of noncancerous bone diseases, encapsulation in particles or as generator of  $^{212}\text{Pb}$ .

$^{223}\text{Ra}$  decays to  $^{219}\text{Rn}$  (3.96 s),  $^{215}\text{Po}$  (1.78 ms),  $^{211}\text{Pb}$  (36.1 min),  $^{211}\text{Bi}$  (2.14 min),  $^{207}\text{Tl}$  (4.77 min) or  $^{211}\text{Po}$  (0.52 s) and stable  $^{207}\text{Pb}$ . This long disintegration sequence generates four high energy  $\alpha$  particles, two  $\beta^-$  particles and  $\gamma$  rays conducting to a total energy emitted around 28 MeV. The cascade of  $\alpha$  particles generated (around 96% of the total energy) allows to increase the radiation dose received by the targeted tissues, whereas low energy  $\gamma$  component (269 keV) is of interest for monitoring (Figure 8).

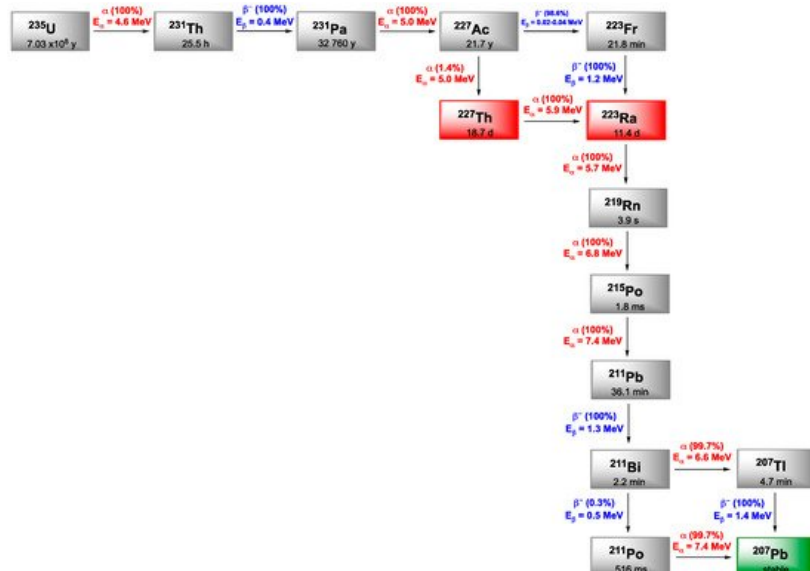


Figure 8. Decay schemes for the production of  $^{223}\text{Ra}$  and  $^{227}\text{Th}$ .

## 7. Terbium-149

Terbium is a rare-earth metal with only one stable isotope,  $^{159}\text{Tb}$ , whose physico-chemical properties are interesting for the development of fluorescent complexes. This element is also described as the “Swiss army knife of nuclear medicine” because among its thirty-six isotopes reported, four of them exhibit suitable properties to cover all modalities in nuclear medicine:  $^{152}\text{Tb}$  (17.5h,  $E_{\beta^+} = 1.08$  MeV) for positron emission tomography (PET),  $^{155}\text{Tb}$  (5.32d,  $E_\gamma = 86.55$  keV) for SPECT and Auger electron therapy,  $^{149}\text{Tb}$  (4.1h,  $E_\alpha = 3.97$  MeV) and  $^{161}\text{Tb}$  (6.89 d,  $E_\beta = 0.154$  MeV) for therapy.  $^{149}\text{Tb}$  decays to several radiolanthanides by emission of low energy  $\alpha$  (3.97 MeV, 17%), electron capture (76%), and  $\beta^+$  particles emission (730 keV, 7%), making it interesting for TAT and a possible follow-up by PET. It has to be mentioned that the potential radiotoxicity of the daughter isotopes (long half-life) generated is still to be determined (Figure 9).

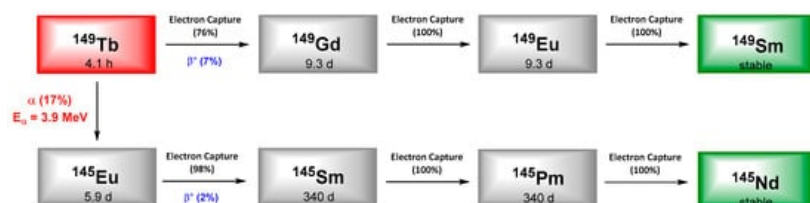


Figure 9. Decay scheme of  $^{149}\text{Tb}$ .

## 8. Thorium-227

Thorium is a metal of the actinide series whose isotopes are all radioactive. Natural thorium exists almost exclusively as  $^{232}\text{Th}$  and to a lesser extent  $^{230}\text{Th}$ . Thorium isotopes exhibit mostly very short (few  $\mu\text{s}$  or ms) or long (few years) half-lives and only two exhibit a potential for TAT:  $^{226}\text{Th}$  (30.6 min) and  $^{227}\text{Th}$  (18.7 days). Nevertheless, due to a difficult production process (from  $^{230}\text{U}$  decay), availability of  $^{226}\text{Th}$  remains presently anecdotal with respect to the amount needed for research, and  $^{227}\text{Th}$  emerged as the most promising candidate.