Invited Paper

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The Radiochemical and Radiopharmaceutical Applications of Radium

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Abstract: This review focuses on the chemistry and application of radium isotopes to environmental monitoring, analytical, and medicinal uses. In recent years, radium has been used primarily as a tracer to study the migration of radioactive substances in environmental systems. Tracing the naturally occurring radium isotopes in mineral and water sources allows for the determination of source location, residence time, and concentrations. An understanding of the concentration of radionuclides in our food and water sources is essential to everyone’s health as alpha particle decay is highly damaging in vivo. Due to this high radiobiological effectiveness, there is increased interest in using alpha-emitting radionuclides to prepare new, therapeutic radiopharmaceutical drugs. Selected studies from the recent literature are provided as examples of these modern applications of radium isotopes.

Keywords: Alpha emitters, Radium, Radiochronology, Radiotracers, Radiotherapy

1 Introduction

In December of 1898, Marie and Pierre Curie announced the discovery of a second element found in the uranium-extracted residues of pitchblende ore and, due to the intense radiation rays it emitted, it was named radium [1]. Interestingly, radium was independently discovered by Friedrich Giesel shortly after the Curies in early 1899 and he then proceeded to develop an industrial fractional crystallization method to better enable its use [2]. The discovery of radium brought radioactivity to the attention of the general public and inspired many new uses of radioactivity. During the first half of the 1900s, radium saw utility in some interesting commercial ways including luminescent paint for watch dials [3], a spinthariscope for counting alpha scintillations [4], radium toothpaste to strengthen teeth [5], radium cosmetics [6], and even a radium suppository to “increase vitality in men” [7]. One notorious example was Radithor, which was marketed as “a cure for the living dead”; the solution was guaranteed to contain 1 µCi (37 kBq) each of $^{226}$Ra and $^{228}$Ra [8]. We now know this was just a dangerous gimmick, but the prospect for medical applications was immediately noted for radium. Henri Becquerel received a skin burn from a vial of radium that he carried in his pocket; afterwards Pierre Curie performed experiments on his own skin to confirm this effect and reported that radium could have medicinal applications. Early attempts at radiation therapy utilized sources of radium salts to treat a variety of ailments including: uterine cervical cancer, arthritis, skin lesions, lupus, and throat cancers [9]. Now that we have an increased understanding of alpha radiation and the decay mechanisms of the various radium isotopes, safer practices have been put into place and radium has been substituted by alternative nuclides for most uses. The purpose of this review is to provide a general discussion on some of the modern applications of radium isotopes, including bio- and geochronology, hydrogeochemical analysis, emanation thermal analysis, and radiopharmaceutical applications.

1.1 Radium and its fundamental chemistry

Radium is the heaviest known member of the group 2 elements, the alkaline earth metals. It is only found in very low abundance (approx. 0.1 ppt) as a trace element in uranium and thorium minerals [10]. Marie and Pierre Curie isolated radium from the residue of pitchblende ore after uranium extraction found in Joachimstal, Bohemia and it required several tons of the pitchblende residues to recover approximately 0.1 gram of radium [11]. It is now
found in higher yielding sources, including carnotite sands in Colorado, and uranium ore in both the Republic of Congo-Kinshasa and the Great Bear Lake region of Canada [12]. Additionally, the possibility of recovering radium from uranium processing waste has been noted if the practice was permitted [13].

The chemistry of radium is analogous to barium, which is commonly used as a surrogate due to the intense radiation of radium. Radium metal is soft and a lustrous, silver-white color, but it is never found in nature as the pure metal, as it is highly reactive and rapidly reacts with nitrogen in air to form the black layer of radium nitride, $\text{Ra}_3\text{N}_2$ [13-16]. Additionally, the metal readily reacts with water to produce hydrogen gas and radium hydroxide, $\text{Ra}(	ext{OH})_2$, and although the second ionization enthalpy is nearly double the first (509 and 979 kJ mol$^{-1}$), it is still quite low and thus radium is exclusively found in the $+2$ oxidation state in aqueous conditions [14,15]. This results from the high lattice energies in the solid salts and the high hydration energies of the $\text{Ra}^{2+}$ ion [13]. As a result, radium exhibits a highly basic character and is difficult to complex. Therefore, most radium compounds are simple ionic salts.

Quantitative data on radium compounds is limited due to its radioactive nature and scarce availability [13-19]. Some of the frequently referenced radium salts are listed in Table 1. These salts mostly form white crystals, but chloride salts that were co-precipitated with barium chloride have been noted to exhibit a rose tinted color due to the barium impurities within the crystal lattice. Though they are fairly stable to radiolysis, the salts degrade and darken over time as a result of radiation damage and secondary electrons from the alpha decay can interact with nitrogen in the air causing these salts to luminesce. The only compounds of radium that are commercially available are radium chloride and radium bromide. Both the chloride and bromide are highly soluble in aqueous conditions, but they will precipitate with increased concentration of their mineral acids. Both are slightly less soluble than their respective barium analogues, which have been utilized to isolate radium by fractional crystallization. Though the separation is more efficient using the bromides, the chloride is more frequently used due to material costs. Radium nitrate is also soluble in aqueous conditions, though not as well as the halides. It does become highly insoluble in high acid concentrations (80% HNO$_3$), which is useful to separate radium from other elements. Additionally, radium can be isolated by precipitation as one of its insoluble salts (i.e. radium sulfate or carbonate). Radium sulfate is highly insoluble in aqueous conditions and can be used to selectively precipitate radium by adding sulfuric acid to a soluble salt. Most metals will remain dissolved in sulfuric acid, but radium sulfate will precipitate once the acid is diluted. Radium carbonate is insoluble in water, but will readily dissolve in dilute acids, which can easily separate radium from water soluble contaminants.

### 1.2 Isotopes of Radium

There are 34 known isotopes of radium, with mass numbers ranging from 201 to 234 [20]. All of the isotopes are unstable and decay with half-lives ranging from nanoseconds to thousands of years. Only four isotopes of radium are naturally occurring ($^{223/224/226/228}\text{Ra}$) and are found as part of the decay chains of primordial $^{235/238}\text{U}$ and $^{232}\text{Th}$ [20-22].

Radium-226 is a pure alpha emitter produced as part of the $^{238}\text{U}$ decay chain (Fig. 1) and it is the most stable and most abundant isotope of radium. It has a half-life of 1600 years, a maximum alpha particle energy of 4.78 MeV, and a traceable gamma emission at 186.2 keV (3.64 %). It decays via a series of nine daughter nuclides emitting five alpha particles and four beta particles to finally become stable $^{206}\text{Pb}$ [20-22]. The long-lived half-life makes it extremely useful for many environmental applications such as radiometric dating, evaluating exchange between groundwater and surface water, and determining retention times of water sources.
Radium-223 is a pure alpha emitter produced as part of the $^{235}$U decay chain. It has a half-life of 11.43 days, a maximum alpha particle energy of 5.87 MeV, and an abundant gamma emission at 269.5 keV (13.9%). It decays via a series of six daughter nuclides emitting four alpha particles and two beta particles to finally become stable $^{207}$Pb [20-22]. The relatively rapid succession of daughter nuclides decay has led to the use of $^{223}$Ra in radiopharmaceutical applications. It is also used in environmental applications as a comparator for $^{238}$U composition in source rock and water sources.

Radium-228 and radium-224 are produced as part of the $^{232}$Th decay chain. Radium-228 is a pure beta emitter with a half-life of 5.75 years and a maximum beta particle energy of 39.5 keV. It decays via a series of three daughter nuclides emitting an alpha particle and two beta particles to become $^{224}$Ra. The longer-lived $^{228}$Ra finds use in radiometric dating applications. Radium-224 is a pure alpha emitter with a half-life of 3.66 days, maximum alpha energy of 5.69 MeV, and a relatively abundant gamma emission at 241.0 keV (4.10%). It decays via a series of six daughter nuclides emitting four alpha particles and two beta particles to finally become stable $^{208}$Pb [20-22]. Due to its relatively short half-life, $^{224}$Ra was used in radiopharmaceutical applications until 2005, but this was stopped due to indiscriminate targeting of healthy tissue. Additionally, the relationship with its gaseous daughter, $^{220}$Rn, has led to use of $^{224}$Ra in emanation thermal analysis. The existence of a long-lived and short-lived radium isotope in the same decay series has enabled the study of radioactive disequilibrium in water sources, sedimentation, and source rocks.

## 2 Radiochemical Applications

The relative natural abundances, differences in parent and daughter chemistries, and the distinctly varied decay characteristics of the naturally occurring radium isotopes make them useful for evaluating natural phenomena such as volcanic rock formation, groundwater exchange with surface water, continental and coastal water mixing, distribution of nutrients in water sources, and radioactivity accumulation in animals and water sources.

As illustrated in Figs. 1-3, the decay of the primordial radionuclides $^{235/238}$U and $^{232}$Th involves series of radionuclides with varied half-lives and chemical properties [20-22]. In an undisturbed system, all of these radionuclides are in a state of secular equilibrium, meaning the rate of decay is equivalent for all members of a given decay chain [23]. However, this equilibrium is often disrupted in nature due to the varied reactivity of the different elements (U, Th, Ac, Ra, Po, and Pb) leading to a state of radioactive disequilibrium. This occurs when a long-lived parent nuclide is removed from the
source leaving the daughter nuclides to decay with their characteristic half-lives or a daughter nuclide is removed and begins to grow back in from parent radionuclide decay until the equilibrium is reestablished [24]. Measurement of this disequilibrium can provide information about the time since removal and the chemical fractionation in the biological or geological source.

2.1 Using radium chronometers for radiometric dating

There are several radium chronometers that are useful for radiometric dating but the most commonly evaluated relationship for geological processes is between $^{226}$Ra and its parent $^{230}$Th. The determination of time is based on the in-growth of $^{226}$Ra after the isolation of $^{230}$Th in a source material. The significantly longer-lived $^{230}$Th ($754 \times 10^4$ a) slowly decays into the shorter-lived $^{226}$Ra (1600 a) and the disequilibrium of $^{226}$Ra/$^{230}$Th provides a measure of time since the isolation of $^{230}$Th. In an ideal scenario, the $^{226}$Ra/$^{230}$Th system would be isolated from outside $^{230}$Th sources and increase solely from $^{226}$Ra in-growth. Once equilibrium is established, the chronometer no longer provides an accurate measure of time, but can still provide a minimum time since disequilibrium occurred [25]. The geologically short half-life of $^{226}$Ra restricts its usage to samples that are less than 8000 years old, but this still allows for the accurate dating of recent natural events.

Several studies have utilized U/Th chronometers including $^{226}$Ra/$^{230}$Th to evaluate the age of volcanic rock formations [26-28]. The heterogeneity of magma has been well studied and established [29], which means that crystals within the magma may be significantly older than the eruption event. Plagioclases are silicate-based minerals that are a major constituent of the earth’s crust. Recently, Eppich et al. [26] demonstrated the existence of significantly older plagioclase in two distinct samples of dacitic magma from Mount Hood, Oregon, USA from the Old Maid (approx. 215 a) and Timberline (approx. 1500 a) eruption events. The average $^{226}$Ra/$^{230}$Th age estimates showed that the plagioclase crystals within the magma were $> 4500$ a (Timberline) and $> 5500$ a (Old Maid), which are significantly greater than the eruption periods. Additionally, the cores of the crystals were shown to be $> 10000$ years old for both populations. Therefore, it was demonstrated that these plagioclase crystals must reside in the sub-surface for several eruption events until inclusion by interaction with mafic recharge magma. Another recent example given by Waters et al. [27] used U/Th chronometers including $^{226}$Ra/$^{230}$Th and $^{206}$Pb/$^{208}$Pb to evaluate axial and off-axis lava flows for overlapping spread centers on the East Pacific Rise. Examination of the various chronometers provided several valuable pieces of information. First, all samples taken for this study exhibited $^{230}$Th and $^{226}$Ra excess suggesting these formations are quite young ($< 8000$ a) except for a few dacite samples. Additionally, samples of the axial basalts and basaltic andesite lavas exhibited $^{206}$Pb/$^{208}$Ra disequilibria and therefore had to erupt within the past 100 years. The composition of these samples also confirms that the most recent volcanism occurred within the axial region. Interestingly, some older dacites were found to have $^{226}$Ra/$^{230}$Th equilibrium which would place them at $> 8000$ years old, while some intermediate compositions were found to be quite younger. It was postulated that off-gassing of $^{222}$Rn from basaltic magma may have been trapped under the more viscous dacite magma creating a frothy region. The density imbalance of this region may have led to magma mixing and lava of intermediate compositions. This study demonstrates the diverse information possible from radiometric dating.

An interesting usage of radiometric dating is the study and age estimation of fish populations, which provides a quantifiable metric to the deep sea fishing industry and could assist in determining overfishing. Understanding the age of maturity and overall longevity for a given species is necessary for proper management of fisheries. For fish, $^{226}$Ra is accumulated from the aquatic environment and, due to its chemical nature, it will deposit into the calcium carbonate crystal lattice as the otoliths form. Otoliths (ear stones) are layered structures of calcium carbonate and a gelatinous matrix that form throughout a fish’s life. As with the previously mentioned $^{226}$Ra/$^{230}$Th ratio, $^{226}$Ra will decay into the relatively short-lived $^{206}$Pb (22.20 a) and this in-growth can be measured to determine the age of the fish. Studies of several fish populations have been published including golden tilefish [30], Antarctic toothfish [31], Pacific grenadier [32], orange roughy [33], yelloweye rockfish [34], and opakapaka (pink snapper) [35]. Age determinations are based on the disequilibrium within first few years of growth by determining the $^{206}$Pb and $^{208}$Pb activities in samples are taken from the core of otolith for each fish sample. Core samples are used to keep the method consistent across all age populations. Additionally, comparisons are made to whole otolith of juvenile fish of a known age as an external standard. In many cases, radiometric dating was used as a validation of the traditional age determination using microscopic analysis of the calcium carbonate growth zones.
For the golden tilefish (26 a), Antarctic toothfish (39 a), and Pacific grenadier (56 a), the traditional age determination method seemed well within agreement with the radiometric dating. However, in some cases, the traditional age determination method is not always valid. The opakapaka does not exhibit well-defined annual growth zones, which has led to great uncertainty for the longevity of this species by traditional age determination methods. Previous measurements placed the maximum observed age at 18 years, but $^{210}$Pb/$^{226}$Ra dating showed this species could live significantly longer (45.6 years mean age of the largest fish). Understanding this critical difference in life span could help ensure sustainable fishing practices since some of these longer-lived fish take more time to mature and contribute to reproduction. $^{210}$Pb/$^{226}$Ra dating is restricted to time’s up to about 100 years due to the 22.20 year half-life of $^{210}$Pb. As these nuclides approach equilibrium and the ratio approaches 1, the method is limited to implying that the ages are greater than 100 years. The experimental data for both the yelloweye rockfish and orange roughy demonstrated centurion life spans in several samples. For the orange roughy, the longevity has been a source of controversy. The study provided by Andrews et al. demonstrated a long lifespan of 93 year for the older specimens using $^{210}$Pb/$^{226}$Ra dating [33]. This data could help to support previous studies stating the longer life span and invalidate studies claiming shorter lifespan, which has resulted in overfishing and decimation of the orange roughy population. Similarly, the establishment of a centurion lifespan for the yelloweye rockfish can influence policy and prevent overfishing of this population.

2.2 Use of radium isotopes as natural tracers in hydrogeochemistry

In addition to the relationship between radium and other members of their decay series, the relative abundance of the naturally occurring radium isotopes can also be highly variable in geological systems. Several of these relationships have been studied in depth. The relationships between the short-lived isotope $^{223,224}$Ra and the long-lived $^{226,228}$Ra provide information on the age of a distinct water source [36-39]. Since $^{223}$Ra and $^{228}$Ra are members of the same decay series (Fig. 3), the relative ratio of these isotopes is not influenced by the parent nuclide concentration in the source rock for a system in equilibrium, but by daughter recoil. Due to the affinity of $^{229}$Th for particulate matter, $^{228}$Ra is usually trapped within or on the surface of the particulate, thus variation of the $^{228}$Ra/$^{226}$Ra ratio results from daughter recoil out of the particulate or source rock. In a system immediately downstream of radium precipitation or recently recharged waters, the short-lived $^{220}$Ra (3.63 d) will reach equilibrium in the water much quicker than the longer-lived $^{226}$Ra (5.75 a), resulting in higher values for the $^{226}$Ra/$^{228}$Ra ratio. Additionally, $^{223}$Ra and $^{228}$Ra decay from two different uranium isotopes ($^{233}$U and $^{238}$U, respectively). From this relationship, it would be expected that the ratio of $^{223}$Ra/$^{226}$Ra would match the $^{233}$U/$^{238}$U ratio (0.046) as the source mineral under steady state conditions. However, similar to the $^{226}$Ra/$^{228}$Ra ratio, downstream from a recharge point or Ra precipitation, the $^{223}$Ra/$^{226}$Ra will be higher due to the slower in-growth of $^{226}$Ra, providing a marker for water turnover for a given water source and the disequilibrium from the anticipated ratio can be used to calculate the time since water discharge or radium precipitation.

As water travels into coastal waters from their continental sources, the shorter-lived $^{223,224}$Ra isotopes rapidly decay leaving only the longer-lived $^{226,228}$Ra isotopes. Studying the abundance of each radium isotope at various locations within a water source can provide insight as to the transport of these isotopes through the water source. This can be used to evaluate and identify sources of groundwater exchange with surface water, discharge of continental waters into coastal waters, and water retention times [40]. Recently, many studies focused on the introduction of radium isotopes into coastal water as a marker to better understand the incorporation of nutrients and freshwater by submarine groundwater discharge [41-45]. Sanial et al. [41] used the relationship between $^{223,224}$Ra to understand the source and timescale of iron and other micronutrient input into the Southern Ocean off the Kerguelen Islands. Sampling was performed at various depths and that $^{228}$Ra activity increased with increasing depth, while $^{223}$Ra activities were high near the seafloor and surface and below detection limit activities at intermediate depths. This suggests that vertical mixing only plays a minor role in the incorporation of micronutrients in the short-term. The high $^{223}$Ra activity levels at the surface could only be from interaction with shallow sedimentation suggesting that horizontal advection plays a major role in nutrient transport. Additionally, the $^{224}$Ra/$^{223}$Ra ratio was evaluated at several locations to determine timescale for the dispersion of radium from its origin on the northern Kerguelen Plateau and off-shore and found that radium was rapidly transported with a short time of four to eight days. In a similar study, Stewart et al. [42] demonstrated the importance of submarine groundwater discharge for providing nutrients and dissolved carbon into Moreton Bay,
Australia. Surface water and groundwater samples were taken from several locations at several depths around the bay to determine the flow of radium and dissolved carbon. It was found that the short-lived $^{223/229}$Ra were found near the shore in four major hotspots, while they were below detection limits near the center of the bay. Using the $^{226}$Ra/$^{232}$Ra chronometer, the residence time of the water in the bay was determined to be approximately 40 days, which is comparable to a previous hydrodynamic model value of 50 days. The major source of $^{228}$Ra was shown to come from submarine groundwater discharge, which contributed approximately three times the $^{226}$Ra than all of the freshwater sources combined. Dissolved carbon was estimated to be 20-38 times higher in groundwater sources than in the surface water sources. The results of this study showed the important role of submarine groundwater discharge in the nutrient profile of Moreton Bay.

Another interesting, although complex, relationship for identifying source waters and minerals is between $^{226}$Ra and $^{228}$Ra. The abundance of these isotopes in a system is proportional to the $^{238}$U and $^{232}$Th content in the source rock, but variation occurs due to the mobility of uranium and thorium into water sources via erosion and sedimentation. For example, uranium is highly mobile in oxidized water sources and tends to form soluble carbonate and phosphate complexes, while thorium will preferentially bind to particulate or remain in the source mineral. For this reason, samples from carbonate sources will have a high $^{226}$Ra/$^{228}$Ra ratio, while silicate sources are typically closer to 1:1 [24,36,37]. Another factor affecting their presence in a system is the relative rates of daughter recoil. With a given alpha particle emission, a daughter nuclide may recoil as much as 100 nm [23]. This significant shift could eject atoms near the surface into the water source. For a given system, equilibrium will be reached for the relative recoil rates. This recoil equilibrium can be used to identify young water sources, because $^{228}$Ra (5.75 a) will accumulate much quicker than $^{226}$Ra (1600 a).

### 2.3 The use of radium in emanation thermal analysis

The decay of radium to its inert, gaseous radon daughter enables the use of emanation thermal analysis. Emanation thermal analysis uses radioactive emissions to evaluate the physical changes in material as a function of temperature [46]. A material (i.e. mineral, metal, or glass) is coated with a solution containing $^{228}$Th and $^{226}$Ra. The recoil daughters from their decay impregnate the material with radionuclides, and will eventually reach a state of equilibrium. The activity is measured at room temperature to set a base line for radon diffusion from the coated material, and then it is heated while monitoring the release of radon. In a system where the material undergoes a physical change, a corresponding change in the release of radon is noted. This measurement allows for materials to be evaluated for performance under thermally stressful conditions/environments. Previous literature used this method to examine the permeability of minerals such as quartz [47] and clay [48]. In both studies, an increased diffusion of radon was noted at lower temperatures due to water loss as the crystal dehydrated. Due to the similarity in size of radon and water (1.34 and 1.40 Å, respectively), it was believed the increased diffusion resulted from the reorganization of the crystal while losing water.

Recently, Balek et al. [49] have utilized emanation thermal analysis to study the diffusion of radon from anthropogenic analogues of vitrified nuclear waste, which can provide an understanding of the long-term behavior of these materials. To evaluate the potential loss of radioactive materials due to microstructural changes caused by aging and weather, uranium glass produced in the Czech Republic was tested as an example study. The samples had been buried for 50 years. The glass was used “as is” for the weathered samples, while other samples had the weathered surfaces laser ablated to pose as “like new” samples. The study concluded that the two groups behaved similarly at temperatures below 300°C, meaning that weathering had little effect on the retention of radionuclides under the conditions expected in a nuclear waste depository.

### 3 Radiopharmaceutical Applications

Short-lived, alpha-emitting radionuclides, such as $^{223/229}$Ra, have great potential for use in therapeutic radiopharmaceuticals. Alpha particles are highly energetic (4–9 MeV), relatively large in size, and have a high charge-to-mass ratio, which allows them to readily interact with surrounding matter and frequently create ionization events along their path [50,51]. This high frequency of ionization events translates to alpha particles exhibiting a high rate of linear energy transfer (LET) of approximately 100 keV μm$^{-1}$. For this reason, alpha particles are highly destructive in vivo over a very short range (up to 100 μm). Additionally, the mechanism of action in a cell is more destructive than beta particles, gamma rays, or x-rays. Alpha particles typically act directly on DNA by inducing double strand breaks, which destroys the template for DNA replication and repair, making it impossible
for the cell to recover [52,53]. Due the high LET and effective destructive mechanism, the relative biological effectiveness (RBE) of alpha particles is 20 compared to a value of 1 for beta particles, gamma rays, and x-rays. The effectiveness and small, targeted deposition range makes alpha particle therapy an exciting alternative to other radiotherapies. This section of the review focuses on the clinical application of radium and recent research literature for expanding its use.

3.1 $^{223}$Ra radium chloride for treatment of metastatic castration resistant prostate cancer

Prostate cancer is a frequently occurring disease affecting about 1 in 7 men worldwide [54–56]. Progression of the disease can lead to an advanced diseased state known as metastatic castration resistant prostate cancer (mCRPC), which is incurable with a median, untreated survival time of 11.3 months [57]. At this point, treatment is directed towards attempts to enhance survival and comfort. The primary source of discomfort and pain is associated with the development of bone metastases. For this reason, radiotherapeutic treatments have been developed to shrink or eliminate these metastases.

In 2013, $^{223}$Ra radium chloride (Xofigo®; formerly alpharadin) became the first and only alpha-emitting radiopharmaceutical to receive FDA and EMEA approval for clinical use, with an intended purpose to treat metastases associated with mCRPC. A series of six intravenous injections (50 kBq kg$^{-1}$, $^{223}$RaCl$_2$) is administered with each injection separated by four weeks [58]. Once in the body, $^{223}$Ra$^{2+}$ will function as a Ca$^{2+}$ mimic and complex with the bone mineral hydroxyapatite at sites of actively growing bone, which occurs at an accelerated rate within metastatic bone tissue [14,53,58,59]. As mentioned previously, $^{223}$Ra and its daughters release four alpha particles and two beta particles before ending at $^{207}$Pb (Fig. 2); this delivers a large, cumulative dose of ionizing radiation (28 MeV) over a short range (< 10 cell diameters), damaging the DNA of cells within the targeted range, and ultimately killing the metastatic cells [53,58,59].

The effectiveness of Xofigo® was demonstrated in Phase III clinical trials performed from 2008 to 2011 [53,57,59,60]. 921 patients with confirmed cases of mCRPC participated in a double-blind randomized trial with two patients receiving treatment for everyone in the placebo group. The patients received a series of six intravenous injections containing 50 kBq kg$^{-1}$ doses of $^{223}$Ra with four weeks between each injection. Patients receiving the treatment with $^{223}$Ra exhibited a 3.6-month prolonged survival time over the placebo group and a 5.8 month improved timeframe before the occurrence of a systematic skeletal-related event (i.e. spinal compression or pathological fracture) with a reduction of occurrence of spinal compression [61]. Minimal side effects were noted with this drug and unintended dose to other organs was limited, with distribution studies showing less than 2% of the daughter nuclides migrate away from the bone surface [59,60,62].

3.2 $^{224}$Ra radium chloride for treatment of ankylosing spondylitis

Ankylosing spondylitis (AS) is a systemic inflammatory rheumatic disease that affects as much as 0.1–1.4% of the world population, with men being three times more likely to develop the disease [63]. Additionally, it usually presents in mid-twenties, but can affect children as well. This disease is highly debilitating and can cause vertebrae in the spine to fuse together, reducing flexibility, and affecting posture [63].

Starting in 1948, $^{224}$Ra radium chloride was used to treat AS in Germany [64]. The majority of patients received a series of 10 weekly injections with a cumulative dose of approximately 50 MBq. Treatment of AS with $^{224}$Ra continued until 1990, and then was re-approved using a lower dose of $^{224}$Ra from 2000 to 2005 [65–67]; a series of 10 weekly injections was given with a cumulative dose of about 10 MBq. Good clinical results were reported for AS patients, describing a long-lasting benefit with a reduction in the need of anti-inflammatory and analgesic drugs.

However, long term effect studies reported an increase in risk of myeloid leukemia for patients treated with $^{224}$Ra with a particularly high rate of occurrence for patients treated while under the age of 21 [68,69]. In the largest study, Wick et al. [69] reported epidemiological findings for a group of 1471 patients treated with $^{224}$Ra between 1948 and 1975. The follow-ups were performed approximately 25 years (median). Causes of death had been determined for 1006 treated patients and 1072 within a control group. An incident rate of leukemia greater than 1.5 times higher was reported for the treated group versus the control group (19 compared to 12). A very disproportionate amount of the cases occurring were myeloid leukemia (11 occurred with 2.9 expected).
3.3 Radium and targeted alpha therapy

Several reviews have discussed the use of alpha-emitting radionuclides in medicine [70-72]. The current review will specifically focus on the current trends and present use of radium in radiopharmaceutical applications. A growing trend in medical oncology is personalized and targeted medicine. Current research into alpha-emitting radiopharmaceuticals is focused on the development of targeted therapy drugs. The goal of targeted alpha therapy is the incorporation of the radionuclide into a targeting moiety specific to the tumor to increase the efficacy at the target site, while reducing the damage to the surrounding healthy tissues. The urgent need for these specific-binding moieties was highlighted by the issues with the use of $^{223}$Ra radium chloride; the non-specific attraction of Ra$^{2+}$ to all actively growing bone is highly problematic and lead to uptake not only at the site of AS, a non-cancerous disease, but healthy bone tissues as well.

As previously discussed, radium is particularly difficult to complex due to its electronic structure, which has limited its therapeutic application to its simple salt, RaCl$_2$. Several studies evaluated the capacity for macrocyclic ligands to form stable radium complexes and to attach targeting moieties to radium. Henriksen et al. [73] tested 1,4,7,10-tetraazacyclododecan-1,4,7,10-tetraacetic acid (DOTA), diethylenetriaminopentaacetic acid (DTPA), 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (Kryptofix 2.2.2), and 5,11,17,23-tetraazabicyclo[8.8.8]hexaspiro[12.12]tridecatrien-5,11,17,23-tetraacetic acid (DOTA). These chelators are illustrated in Fig. 4. Competition extraction experiments were performed for the hydrophilic DOTA, DTPA, and Kryptofix 2.2.2 versus the lipophilic calix[4]arene tetraacetic acid complex to determine relative extraction coefficients. The cyclic chelator, DOTA, was shown to provide a higher extraction coefficient than the open chain, DTPA. This finding is consistent with previous literature, which established that the fixed cavity size of cyclic chelators are more size exclusive and exhibit higher selectivity compared to their open chain equivalents. The larger macrocycles, Kryptofix 2.2.2 and calix[4]arene tetraacetic acid, provided more stable complexes. The calix complex performed the best overall, though the stability under biological conditions was still insufficient for in vivo use. The kinetic stability of $^{223}$Ra-containing calix[4]arene tetraacetic acid was evaluated by mixing the calix-containing organic phase with an aqueous phase containing serum abundant metals (Na$^+$, K$^+$, Mg$^{2+}$, Ca$^{2+}$, and Zn$^{2+}$). After 10 minutes, it was found that 35% of the radium had dissociated into the aqueous phase, this large dissociation of radium highlights the difficulty of radium complexation. Variation of the functional groups could provide a calix complex capable of stabilizing radium in vivo. Recently, a series of calix crown complexes were tested by Chen et al. [74] for their ability to retain alkaline earth metals. The paper showed that ionizable p-tetra-tert-butylcalix[4]arene-1,2-crown ether ligands exhibited good Ra$^{2+}$ selectivity over the lighter alkaline earth metals with moderate-to-high metal loading. The distribution coefficients were determined to be 1000, 120, 34, 0.3, and 0.001 for Ra$^{2+}$, Ba$^{2+}$, Sr$^{2+}$, Ca$^{2+}$, and Mg$^{2+}$, respectively. The kinetic stability of these complexes was also evaluated following a similar method as used by Henriksen et al. and < 5% of the $^{223}$Ra had been extracted after 24 hours. These ionizable calixarene-crown ethers could be used to complex $^{223}$Ra and link it to a targeting moiety. In a recent study, Boston et al. [75] suggested that the replacement of the p-tetra-tert-butyl functional groups with hydrogen could lead to a higher degree of selectivity. Modification of these calix crown complexes could possibly provide a stable chelate for radium.

In general, an additional challenge using alpha-emitters is that the intense energy of the daughter recoil has more than sufficient energy to destroy any chemical bond, which would allow the daughter nuclides to migrate from the tumor site and damage healthy tissues [76]. Recently, interesting research has been performed by several groups to encase radium in a stabilizing vesicle such as a nanoparticle or liposome to prevent the release of daughter nuclides and depositing all radiation at the target site. Piotrowska et al. [77] used functionalized nanozeolites to encapsulate $^{224/225}$Ra for use in targeted alpha therapy. Zeolites are aluminosilicate nanoparticles build up of tetrahedral structures with channels and cages capable of incorporating radium (Fig. 5). They reported
a successful production rate with greater than 99.9% of \(^{224/225}\text{Ra}\) incorporated into the nanozeolite (30–70 nm) and effective daughter retention with less than 0.5% leakage observed. As noted by de Kruijff et al. [70], it was not mentioned if equilibrium had been reached in solution for these studies. Out of an equilibrium state, it is possible that the stability and distribution might be drastically altered.

Liposomes have been investigated by Henriksen et al. to encapsulate and take \(^{223}\text{Ra}\) to a tumor site [78]. They utilized Ca-ionophore A23187 (Fig. 6) to load radium into preformed PEG-liposomes, which were then functionalized with folate-F(\text{ab}')\_2-antibody fragments as a targeting moiety. A high radium loading yield was achieved and stability was demonstrated using serum studies. Jonasdottir et al. [79] transitioned the use of liposome-encapsulated radium into \textit{in vivo} studies using a mouse model. As before, the radium was incorporated into PEGylated liposomal doxorubicin using ionophore mediated loading. Biodistribution studies demonstrated not only a migration of daughter \(^{211}\text{Pb}\) and \(^{211}\text{Bi}\), but free \(^{223}\text{Ra}\) was shown to accumulate on bone surfaces of the skull and femur. It was postulated that the liposomal \(^{223}\text{Ra}\) was cleared from the blood and then metabolized by macrophages in the reticuloendothelial system.

With the difficulty of mitigating migration of the daughter nuclides, Cooks et al. [80-85] actually decided to use the dispersion of the daughter nuclides to their advantage. Diffusing alpha-emitters radiation therapy (DaRT) implants \(^{224}\text{Ra}\)-loaded wire in or near the tumor. Recoil from alpha decay ejects the decay daughters into the tumor, while the \(^{224}\text{Ra}\) remains immobilized in the wire. This method ensures the \(^{224}\text{Ra}\) remains at the tumor site. The alpha particle emissions from the daughters destroy the local tumor, which then provides a large supply of tumor antigens that trigger an immune response. Triggering this immune response was demonstrated in mice recently (Confino et al.) [75] to reduce the recurrence of a tumor by re-inoculation with the same tumor cells. 77% of the population did not redevelop tumors after DaRT compared to 33% for the control group. Additionally, a significant increase in the survival rate was noted for DaRT treated mice (63% for treated vs. 29% untreated). Additional studies have shown the prospect of this therapy for treating squamous cell carcinomas [81], glioblastomas [81], melanoma [81], breast [80], colon [80,81,85], pancreatic [84], prostate [81], and lung cancers [83]. This method does have its drawbacks though. Due to its long half-life, \(^{222}\text{Pb}\) was observed to migrate away from the tumor resulting in a higher dose to several organs, most notably the kidneys and liver [82]. The amount of radionuclide escaped was relative to the size of the tumor; 90% \(^{222}\text{Pb}\) leakage in a 0.1 g tumor, but only 12% in a 2.4 g tumor. Thus again, highlighting the necessity of stabilizing radium and its decay daughters to minimize dose to healthy tissues.

4 Summary

Radium has found utility in many applications since it was isolated by the Curies in 1898. Today, it is an important source for the determination of nutrient and water flow in environmental systems. Additionally, it has been utilized in the radiometric dating of volcanic rock, minerals, and even fish. Since its discovery, radium has been used in medicinal applications and now \(^{223}\text{RaCl}_2\) has become the first alpha-emitting radionuclide to receive FDA and EMEA approval for clinical use. With the growth of targeted alpha therapy, radium will continue to find application for the treatment of various diseases. The current research focus in development of these drugs, not only for Ra but all alpha emitters, is the producing stable chelate systems to keep the radium and its daughters localized at the target site. This review has been provided as a brief overview of the modern uses of radium.
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