

Alpha Emitters for Radiotherapy: Basic Radiochemistry to Clinical Studies _ Part 1

Running title: Alpha Emitters for Radiotherapy

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Word count: 5317

Disclaimer: The authors have nothing to disclose.

Financial support: The authors gratefully acknowledge the Radiochemistry and Molecular Imaging Probe core, which was supported in part by the NIH/NCI Cancer Center Support Grant P30 CA008748. We gratefully acknowledge Mr. William H. and Mrs. Alice Goodwin and the Commonwealth Foundation for Cancer Research and The Center for Experimental Therapeutics of Memorial Sloan Kettering Cancer Center (JSL) and the fellowship from the François Wallace Monahan Fellowship from the JLM Benevolent Fund (SP).

Key words: Radiotherapy, Alpha Emitters, Radiochemistry, Clinical Trials

Learning Objectives: On successful completion of this activity, participants should be able to (1) cite α -emitter families available for therapeutic use and understand their current production limit; (2) consider radiation safety concerns when handling α -emitters; and (3) overcome radiolabeling and daughter redistribution hurdles with the approaches described in this educational review.

Abstract: With a short particle range and high linear energy transfer, α -emitting radionuclides demonstrate high cell-killing efficiencies. Even with the existence of numerous radionuclides that decay by α -particle emission, only a few of these can reasonably be exploited for therapeutic purposes. Factors including radioisotope availability and physical characteristics (e.g., half-life) can limit their wide-spread dissemination. The first part of this review will explore the diversity, basic radiochemistry, restrictions, and hurdles of α -emitters.

Radionuclide strategies for curative therapy, disease control, or palliation are positioned to constitute a major portion of nuclear medicine. The range of available therapeutic radioisotopes, including alpha- (α), beta- (β -), or Auger electron emission, has considerably expanded over the last century (1). Matching particle decay pathways, effective range, and relative biological effectiveness to tumor mass, size, radiosensitivity, and homogeneity/heterogeneity is the primary consideration for maximizing therapeutic efficacy. Beta-emitting radioisotopes have the largest particle path length (up to 12 mm) and lowest linear energy transfer (LET) (~ 0.2 keV/ μm), supporting their effectiveness in medium to large tumors (Fig. 1). While the β -particle long range is advantageous in evenly distributing radiation dose in heterogeneous tumors, it can also result in the irradiation of healthy tissue surrounding the tumor site. Conversely, Auger electrons have high LET (4-26 keV/ μm), but a limited path length of 2-500 nm that restricts their efficacy to single cells, thus requiring the radionuclide to cross the cell membrane and reach the nucleus. Finally, α -particles' moderate particle path length (50-100 μm) and high LET (80 keV/ μm) renders them especially suitable for small neoplasms or micrometastases. A recent clinical study highlighted the ability of α -radiotherapy to overcome treatment resistance to β -particle therapy, prompting a paradigm shift in the approach toward radionuclide therapy (2).

For optimized therapeutic efficacy, the alpha cytotoxic payload is expected to accumulate selectively in diseased tissue and deliver a sufficient radiation dose to tumor sites while sparing normal organs and surrounding healthy tissue. Some α -emitting radionuclides (e.g., radium dichloride) demonstrate intrinsic bone-targeting properties, but most radionuclides require conjugation to carrier molecules for specific delivery to tumor cells. Targeted α -therapy relies on the significant differential targeting properties of a molecular vector in delivering the lethal α -payload to cells expressing higher target

concentrations. Consequently, α -emitting radionuclides have been conjugated to a wide range of biomolecules, antibodies, peptides, small molecules inhibitors, and nanocarriers. Numerous α -conjugates showing promising preclinical outcomes are now being evaluated in clinical trials or salvage therapy studies.

ALPHA-EMITTING ISOTOPE RADIOCHEMISTRY

The α -particle is a naked ^4He nucleus with a +2 charge; its extreme mass compared to that of electrons suppresses deflection of the particle and its track is almost linear. Alpha-particles are monoenergetic with initial kinetic energy between 5 and 9 MeV, yielding a corresponding particle range of 50-100 μm (Fig. 1). Alpha-particles are effective ionizing agents and are classified as high LET. As α -particles cannot be directly imaged *in vivo*, the γ -photons, characteristic X-rays, or bremsstrahlung radiation that accompanies the parent radionuclide's decay are often used for quantifying target uptake, dosimetry, and therapy response.

Complex molecular pathways are initiated when α -particles interact with biological tissue (3). The primary target of high LET radiation is DNA, and a single α -particle track can result in irreparable double-strand breaks (4). Nucleus traversal by α -tracks is correlated to cytotoxicity, while traversal through the cytoplasm results in more moderate radiation-induced effects (4,5). In contrast, β -particle irradiation produces mainly single-strand breaks, exhibiting ~ 500 times lower cytotoxic potency than α -particles (Fig. 1) (3). The "cross-fire" effect is the ability of a particle to induce multiple cell damage to neighboring cells, which offers an advantage in heterogeneous tumors (Fig. 2). Due to the particle range, this "cross-fire" effect is thought to be higher with β -emitters, but recent studies showing significant therapeutic effect of α -particles on large tumor masses question this concept (6-

8). In addition to direct effects, indirect radiation effects have been observed. Radiation-induced bystander effect—when DNA damage occurs in cells surrounding irradiated cells, but not directly exposed to radiation—also contributes to the impact of the α -radiation (6). The mechanism of this effect is not fully understood, but is hypothesized to result from extracellular reactive oxygenated species, chromosomal instabilities, or other abnormalities. Finally, the abscopal effect, resulting from radiation-induced immune response, is characterized by therapeutic response in remote lesions (9). Importantly, compared to β -particle radiotherapy that mainly relies on the formation of reactive oxygen species, cell killing efficiency of α -particle was shown to be independent of cellular oxygenation (10).

Due to the different types of biological damage caused by high and low LET, the relative biological effectiveness factor should be taken into account when performing dosimetry calculations so that the estimated absorbed dose reflects the probability and relative severity of a biological effect (11). Based on *in vitro* experiments, if the chosen endpoint is deterministic (e.g., therapeutic efficacy or toxicity), the relative biological effectiveness ranges from 3 to 7 and should be used when predicting the benefit of α -therapy. If the endpoint is stochastic, such as cancer induction, the relative biological effectiveness for α -particles is approximately 20 (11). Human experience, however, has indicated lower toxicity than expected and highlights the dire need for developing accurate dosimetry measurement techniques for α -emitters.

Alpha-emitting radionuclides with potential applications for radiotherapy are presented below. As most α -emitters are progeny in a common decay chain (or family)—either direct progeny or separated by short half-life radioactive intermediates—we elected

to present radioisotopes of the same family together. Radioactive decay through multiple radioactive progeny is referred as “*in vivo* generator” or “nanogenerator” approach.(12) This approach offers the significant advantage of delivering several cytotoxic radionuclides to the tumor for enhanced toxicity but also conversely suffers from the major hurdle of progeny redistribution.

Astatine-211

^{211}At can be cyclotron-produced by bombarding natural bismuth with a medium-energy α -particle beam (28-29.5 MeV) using the $^{209}\text{Bi}(\alpha,2n)^{211}\text{At}$ reaction (13). Even though the production and purification of ^{211}At is inexpensive, the number of accelerators capable of generating a 28 MeV α -particle beam limits the availability of this isotope (13).

With a half-life of 7.2 h, ^{211}At decays via a branched pathway to stable ^{207}Pb , emitting α -particles via two pathways (Table 1). The ^{211}At -daughter, ^{211}Po , emits K X-rays with its alpha decay, allowing for sample counting and scintigraphic imaging of ^{211}At *in vivo* (14). Astatine belongs to the halogen family and radiolabeling can be performed by adapting radioiodination chemistry (15). Tin precursors and prosthetic groups have been used to label small molecules, peptides, or antibodies (15). The carbon-astatine bond is relatively weak and the release of free astatine can result in undesired toxicity (16). Similar to iodine, free astatine accumulates in the thyroid, stomach, and macrophage-bearing organs such as the spleen and lung.

Actinium-225/Bismuth-213

The current main source of ^{225}Ac comes from ^{229}Th generators ($t_{1/2} = 7.3$ y), which can be “milked” over a three-week period and allows the separation of ^{225}Ra and ^{225}Ac (17). The Oak Ridge National Laboratory ^{229}Th -generator produces up to 33.3 GBq per year.

However, due to the limited number of generators worldwide, there is a severe shortage of this isotope for preclinical and clinical research. The ^{225}Ac shortage also inhibits $^{225}\text{Ac}/^{213}\text{Bi}$ generator manufacturing (18).

Possible pathways to increase ^{225}Ac production include high-energy proton spallation of ^{232}Th . A tri-institutional collaboration among Oak Ridge, Brookhaven, and Los Alamos National Laboratories recently produced millicurie quantities of ^{225}Ac by irradiating a natural thorium target at beam energies between 78-192 MeV(19). Using this method, a ten-day irradiation campaign of a 5 g/cm² thorium target could produce Curie levels of ^{225}Ac (19). The quality of the accelerator-produced ^{225}Ac was equal to that of the ^{229}Th generated; however, the impact of co-produced ^{227}Ac remains to be evaluated (19).

^{225}Ac ($t_{1/2} = 10.0$ d; 5.8 MeV α) decays sequentially through six dominant daughters to stable ^{209}Bi (Table 1). Single ^{225}Ac atom decay yields 4 net alpha and 3 beta disintegrations together with the emission of two useful gamma emissions; it is therefore classified as a nanogenerator (12). The ^{225}Ac -daughter, ^{213}Bi ($t_{1/2} = 45.6$ min; 97.8 % β^- ; 2.2 % 6 MeV α), is a widely studied radionuclide for targeted α -therapy in preclinical and clinical studies. ^{213}Bi forms stable complexes with nitrogen-rich chelators such as CHX-A''-DTPA (2-[p-isothiocyanatobenzyl]-cyclohexyldiethylenetriaminepentaaceticacid) or NETA ({4-[2-(bis-carboxymethylamino)-ethyl]-7-carboxymethyl-[1,4,7]triazonan-1-yl}-aceticacid), and both ^{213}Bi and ^{225}Ac are stable upon coordination by the DOTA chelator (20). Free ^{225}Ac -acetate accumulates primarily in the liver (111.8 ± 2.13 %ID/g) and bone (9.15 ± 1.2 %ID/g)(21). However, once chelated by DOTA, both liver (1.29 ± 0.25 %ID/g) and bone (0.98 ± 0.10 %ID/g) uptake are significantly reduced (21). The ^{225}Ac daughters, ^{221}Fr and ^{213}Bi , will preferentially accumulate in the kidneys and urine.

Thorium-227/Radium-223

^{227}Th and ^{223}Ra are both available upon separation from their mutual parent, ^{227}Ac ($t_{1/2} = 21.7$ d) (22). Clinical production of ^{223}Ra uses $^{227}\text{Ac}/^{227}\text{Th}$ -based generators (23). Parent isotopes are loaded on actinide chromatographic resin and ^{223}Ra chloride solution is obtained after elution with 1M HCl or HNO_3 , subsequent cation exchange column, evaporation, and dissolution in saline solution (24).

^{227}Th ($t_{1/2} = 18.7$ d; 6.0 MeV α -particle) and its daughter ^{223}Ra ($t_{1/2} = 11.4$ d; 5.7 MeV α -particle) act as nanogenerators, releasing up to four high-energy α -particles before reaching stable ^{207}Pb (Table 1). Emission of gamma photons allows for scintigraphic imaging of both isotopes. Biodistribution of ^{227}Th -citrate indicates high uptake in the femur and parietal bone (25). ^{223}Ra is an alkaline earth metal similar to calcium that, like ^{227}Th , preferentially accumulates in sites of bone mineralization, binding into hydroxyapatite. γ -ray spectroscopy of the femur showed that ^{223}Ra redistributes to the bone if eliminated due to the α -recoil energy, resulting in an increased dose to the bone surface (25). The lack of suitable chelating agents to coordinate ^{223}Ra limits the development of radioconjugates. On the other hand, ^{227}Th with its +4 oxidation state can be stably chelated by DOTA (26) and octadentate chelator with 3-hydroxy-N-methyl-2-pyridinone coordinating moieties (Me-3,2-HOPO) (27).

Radium-224/Bismuth-212

^{224}Ra , ^{212}Pb , and ^{212}Bi are produced by generators loaded with their long-lived parent ^{228}Th (28). Severe radiolytic damage to the generators' resin was observed and they were replaced by ^{224}Ra -based generators from which ^{212}Bi and ^{212}Pb are obtained

selectively (29).

^{224}Ra ($t_{1/2} = 3.6$ d; 5.7 MeV α ; 241 keV γ) decays into stable ^{208}Pb , producing four net α -particles and two β -particles, with the main recoil daughters ^{212}Pb ($t_{1/2} = 10.6$ h; 93.5 keV β^-) and ^{212}Bi ($t_{1/2} = 60.6$ min; 36 % 6.1 MeV α) (Table 1). Because of its bone-seeking properties, ^{224}Ra was initially used to treat ankylosing spondylitis (30). Even though ^{212}Pb decays via a β -emission, its longer half-life, as compared to ^{212}Bi , allows for delivery of up to 10 times more dose per unit of administered activity, together with more routine dose preparation and administration. While ^{212}Pb forms stable complex with the DOTA chelator, acid catalyzed dissociation was reported. The TCMC chelator, also referred as DOTAM (1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane), was later developed and demonstrated extremely high stability for the Pb(II) ion (31). During ^{212}Pb decay, γ -ray emissions compete with internal conversion over 30% of the time. The ejection of conversion electrons brings ^{212}Bi to highly ionized states (e.g., Bi^{5+} and Bi^{7+}), destabilizing the bismuth-complexes, and ultimately liberating the radionuclide (32). While free ^{212}Pb accumulates in the blood, liver, bone, and kidneys, ^{212}Bi accumulates mainly in the kidneys and urine.

APPROACHES AND SPECIAL CONSIDERATIONS REQUIRED FOR HANDLING AND ADMINISTRATION OF ALPHA EMITTERS

Since an α -particle of at least 7.5 MeV is required to penetrate the protective skin layer (0.07 mm thick), pure α -emitters do not constitute an external radiation hazard. The main concern is internalization and energy deposition in healthy living tissues (33). Untoward radiation effects to humans related to α -exposure include cancer induction, genetic diseases, teratogenesis, and degenerative changes; the respiratory tract, bone, liver,

and reticuloendothelium system are the most important target tissues (33). The tumorigenesis potential of α -radiation was demonstrated after irradiation of human benign prostate epithelial cells in mice (34). Moreover, mutations and chromosomal aberrations observed in the DNA of cells that received no direct α -particle exposure due to the bystander mutagenic effect, indicate that the current genotoxic risks of α -emitters are underestimated (35).

Proper handling of α -emitters is radionuclide-dependent and each progeny must be considered as periodicity changes with decay. Special monitoring equipment to detect α -particles, such as ZnS(Ag) scintillators, should be available when handling α -emitters, in addition to Geiger-Mueller survey meters (36). Allowable removable contamination levels for α -emitters are about 10 times lower (3.3 Bq per 100 cm²) than for β -emitting radionuclides. A well-ventilated hood or ideally, a glove box, should be used when handling α -emitters with low abundance and low energy γ -emission. If highly energetic γ -rays are emitted during the radionuclide decay, all work should be performed in a shielded hot cell or behind 6" lead bricks using manipulator arms or by adapting remote handling conditions (29). Extra precautions, such as trapping or gas-tight enclosures, should be considered when volatile daughters such as radon are emitted. Double gloving is recommended. Wipe tests should be performed and monitored with a gamma and liquid scintillation counter.

For clinical production, centralized production should be considered for isotopes of appropriate half-lives. Radiochemists should be trained and have access to working and waste storage areas designed for dedicated α -emitting isotope radiochemistry. Clinical doses should be prepared and injected once secular equilibrium is reached. Special considerations for ²²³RaCl₂ preparation, administration, and patient release were reported

in a Phase I clinical study to evaluate ascending doses of $^{223}\text{RaCl}_2$ at Memorial Sloan Kettering (37).

TARGETED ALPHA THERAPY - VECTORS AND RADIOLABELING TECHNIQUES

Targeting moieties for targeted α -therapy include antibodies, peptides, or small molecules; each possesses advantages and pitfalls. Antibodies show favorable biodistribution with high tumor uptake and low accumulation in healthy tissues compared to small molecules. One notable example is prostate-specific membrane antigen small molecule inhibitors (2); accumulation of these small molecule drugs in salivary glands is high while the prostate-specific membrane antigen-specific antibody J591 shows low uptake (38). However, the antibody's longer blood circulation time increases the risk of hemato- and myelotoxicity (6). On the other hand, small molecules and peptides exhibit higher tumor penetration and faster clearance (6). Since targeting moieties have a broad spectrum of pharmacokinetic profiles, it is important to match the therapeutic radionuclide's physical half-life to the vector's biological half-life.

Conjugating a radionuclide to its vector is achieved using either a prosthetic group (^{211}At) or chelate (^{227}Th , ^{225}Ac , ^{212}Pb , $^{213}/^{212}\text{Bi}$). Vectors should be functionalized prior to the radiolabeling and one-step radiolabeling is preferred, especially with short half-life radionuclides. However, the development of α -particle radioimmunoconjugates may require more complex procedures. Radioastatination of antibodies is usually performed using a two-step method, where an aromatic organotin precursor bearing an activated ester is radiolabeled and then conjugated to the antibody (39). Radiolabeling of DOTA-conjugates with ^{225}Ac and ^{227}Th requires harsh conditions (high temperatures, pH extremes) that are not always compatible with sensitive biomolecules like antibodies (26). McDevitt *et al.*

developed a two-step radiolabeling method where an isothiocyanate C-functionalized derivative of the DOTA chelator is radiolabeled and then conjugated to the antibody at 37 °C (40). Although this method suffers from low radiochemical yields (up to 10%) due to the isothiocyanate moiety's hydrolysis. Maguire *et al.* later proposed a one-step method for ^{225}Ac radiolabeling of monoclonal antibodies, allowing for radiochemical yields up to 80% (41) Other approaches imply the development of new chelators that form stable complexes at room temperature. Ramdahl *et al.* reported superior properties with respect to ^{227}Th -radiolabeling and stability using Me-3,2-HOPO compared to the DOTA chelator (27).

Blood toxicity and normal tissue irradiation, due to antibodies' slow kinetic clearance, lead to the development of an alternate delivery approach called *pretargeting*, which separates the targeting vector's administration from the radioisotope (Fig. 3) (42). First, an unlabeled antibody that binds both an antigen and the radioligand is administered, accumulating in the tumor and slowly clearing from the blood and non-targeted tissues. A low-molecular-weight radioligand is subsequently administered and diffuses into the tumor, binding to the antigen-associated pretargeting conjugate. The rapid clearance of any excess radioligand results in improved tumor-to-normal tissue ratios and lower radiation doses to healthy organs (42). Interaction between the pretargeted antibody and the radioligand uses either the extraordinary high affinity of avidin (or streptavidin) for biotin (43), bispecific antibodies (44), or bioorthogonal chemistry (45). This approach combines the advantages of antibodies (e.g., high targeting efficiency, penetration, long residence time) with those of small molecules (rapid clearance). Moreover, this technique allows the association of antibodies with short half-life radionuclides, such as ^{211}At (46) or $^{213/212}\text{Bi}$ (47), increasing their therapeutic potential. Applicability and efficacy in humans, though,

still needs to be proven and the antibody-antigen internalization process should be slow or not occur.

CONTROLLING THE FATE OF THE DAUGHTERS

Upon α -emission, recoil energy imparted to the daughter (100 keV) is about 1000 times higher than the binding energy of any chemical bond, resulting in the daughter's release. Redistribution depends on the distance covered during the recoil process, diffusion processes, and active transport as well as the radionuclide's intrinsic affinity for certain organs. Depending on the daughter's half-life, the time to reach its target and toxicity to healthy organs are impacted. Redistribution of the recoil progeny is extremely difficult to measure and is mostly performed in post-mortem *ex vivo* analysis of organs.

Redistribution of daughters compromised the continuation of the clinical studies using ^{224}Ra . Eight percent of ^{220}Rn , the gaseous ^{224}Ra daughter, was shown to leave the body and high uptake of ^{212}Pb and ^{212}Bi were observed in the red blood cells, kidneys (^{212}Bi), and liver (^{212}Pb) (48). On the other hand, low redistribution was demonstrated with ^{223}Ra daughters in mice and confirmed in humans (49).

Redistribution of ^{213}Bi to the kidneys is a main limitation to ^{225}Ac radiotherapy. Schwartz et al. evaluated the contribution of non-equilibrium ^{213}Bi to kidney dose in mice via gamma ray spectroscopy immediately after tissue harvest, and at secular equilibrium (Fig. 4A) (50). The average absorbed dose to the kidneys was determined to be 0.77 Gy.kBq⁻¹ of which 60% was attributed to non-equilibrium ^{213}Bi excess (50).

The use of α -emitters with short radioactive half-lives and simple decay schemes (e.g., ^{213}Bi or ^{211}At) is an effective solution to daughter redistribution. Nevertheless, the higher cytotoxicity of radioisotopes with longer half-lives and decay through numerous progeny motivated the development of approaches to control the daughters' fate. These include a high degree of nanogenerator cellular internalization. High retention of ^{221}Fr and ^{213}Bi inside LNCaP cells was shown in an internalization study with [^{225}Ac]Ac-J591. Tumor samples revealed 88% retention of ^{221}Fr and 89% of ^{213}Bi at ^{225}Ac secular equilibrium (Fig. 4B) (12).

A second approach relies on the development of a new form of brachytherapy, referred to as diffusing α -emitter radiation therapy. This approach, developed by Arazi *et al.*, involves local administration of wire sources impregnated with radionuclides such as ^{224}Ra in or near the solid tumor tissue (51). Necrotic regions of several millimeters were observed around the therapeutic source in several tumor models (Fig. 4C) (52). Autoradiography showed larger distribution around the source for the later decay daughters, ^{212}Bi and ^{212}Pb , compared to the early decay daughters, ^{220}Rn and ^{216}Po . Redistribution of ^{212}Pb to the kidneys was observed based on tumor size; 90% for 0.1 g tumors whereas only 12% for 2.4 g tumors (51).

Encapsulation of α -emitting radionuclides into nanocarriers was evaluated to retain recoil daughters at the tumor site. ^{223}Ra encapsulation in pegylated liposomal doxorubicin demonstrated sufficient stability *in vitro*. Skeleton uptake remained lower compared to free ^{223}Ra and higher uptake of ^{223}Ra -daughters, ^{211}Pb and ^{211}Bi , was observed in the kidneys (53). ^{225}Ac -doped multi-shell nanoparticles were evaluated to encapsulate ^{225}Ac and daughters (Fig. 4D) (54). Nanoparticles with four GdPO_4 shells followed by gold coating

demonstrated the greatest retention of ^{255}Ac (>99.99%) and its daughters, with up to 98% of ^{221}Fr retained (54).

The use of metal-chelation therapy and diuretics was investigated by Jaggi *et al.* to reduce renal toxicity during ^{225}Ac -radioimmunotherapy (55). Dithiols, known to chelate and enhance the urinary excretion of ^{213}Bi , reduced the renal ^{213}Bi activity as early as six hours post-radiotherapy (Fig. 4E) (55). An increase in ^{213}Bi blood activity was observed in mice but this phenomenon was not observed in cynomolgus monkeys (55). Furosemide and chlorothiazide, two diuretics that inhibit the tubular reabsorption of alkali metals, also significantly reduced ^{221}Fr renal activity (Fig. 4F) (55). Though effective with long circulating biomolecules, such an improvement might not be observed with fast-clearing molecules.

CONCLUSION

The combination of double DNA strand break and indirect cytotoxic effects such as cross-fire or radiation-induced bystander effects provides α -particles with exceptional cell-killing potency. Important caveats for the use of α -emitting radionuclides include production and availability limitations, together with redistribution of daughters. Solutions to these issues are currently being investigated and should therefore allow for more widespread development of α -emitter radiotherapy. Part 2 of this educational review will explore the current preclinical and clinical uses of α -radiotherapy.

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Radioactive particle effects on tumor cells

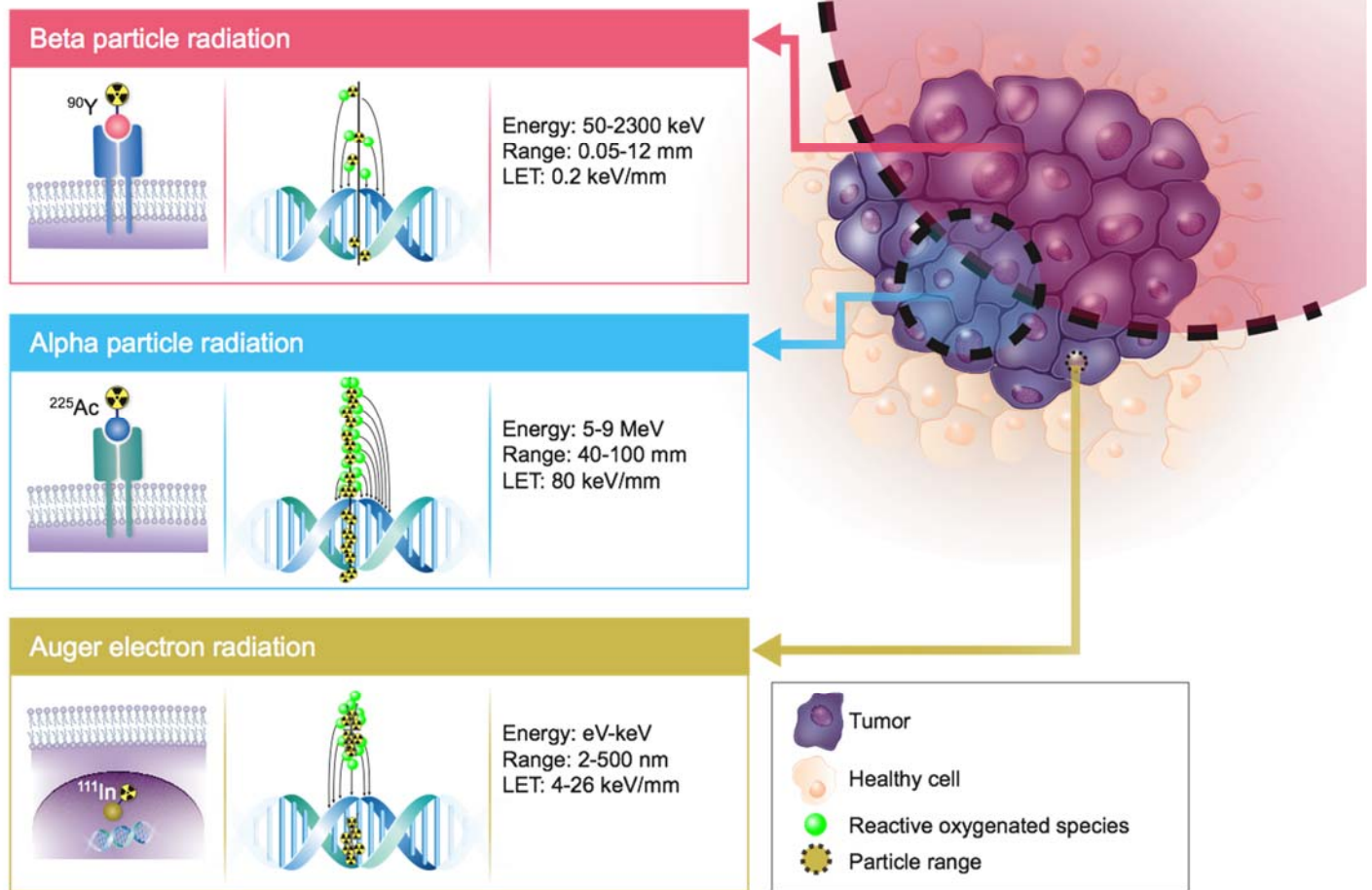


Figure 1. Comparison of therapeutic particles' energies, particle ranges, LET, and DNA damage potencies.

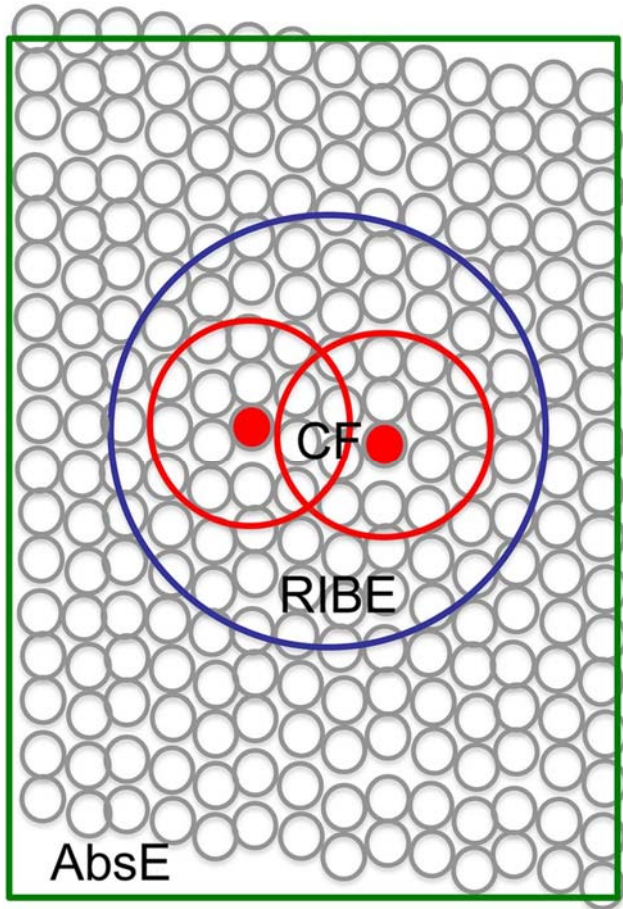


Figure 2: Indirect mechanisms increasing α -particle lethal potency including: the cross-fire effect (CF), the radiation-induced bystander effect (RIBE), and the abscopal effect (AbsE) (6).

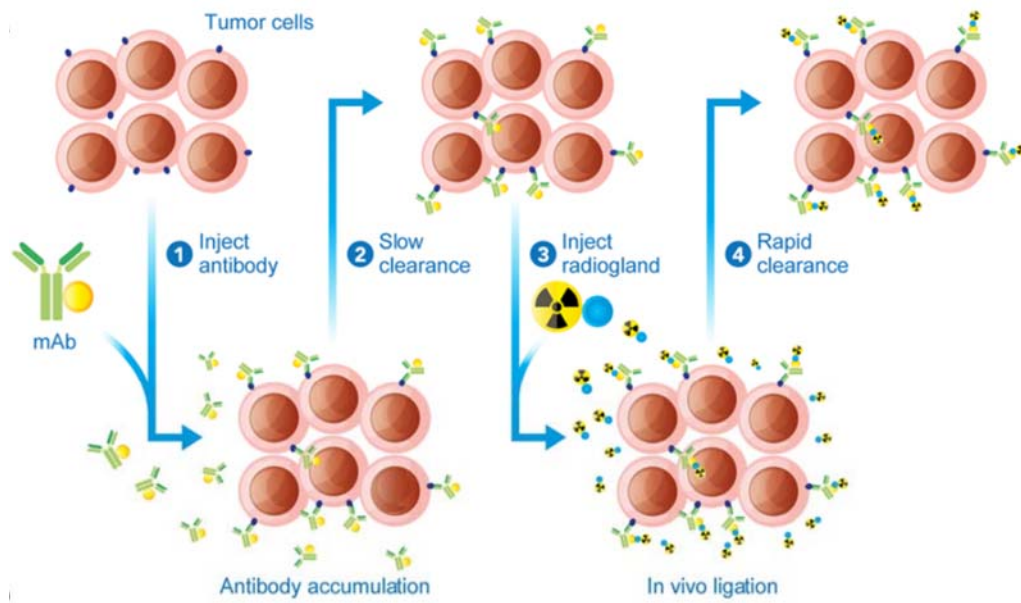


Figure 3. Schematic representation of *in vivo* pretargeting (42).

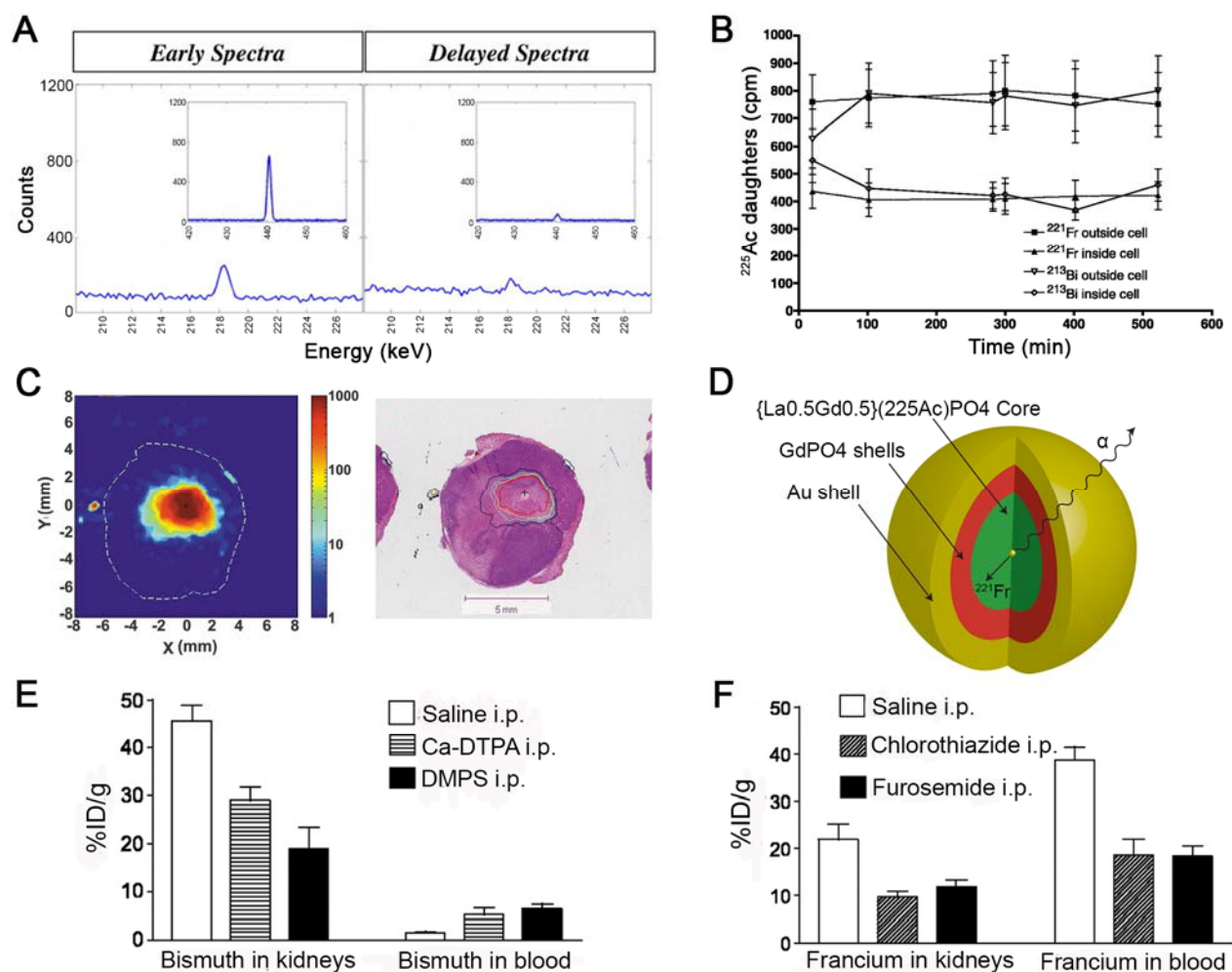


Figure 4. α -emitters daughters' redistribution, approaches to control their fate. A) γ -ray spectroscopy of BALB/C mice kidneys, 96 hours post-injection of ^{225}Ac -HuM195. The different heights of the peak (440 keV) indicate the presence of non-equilibrium ^{213}Bi in the kidneys (50). B) Internalization and retention of ^{213}Bi and ^{221}Fr daughters *in vitro* after binding of ^{225}Ac -J591 in LNCaP cells (12). C) High-resolution autoradiography evaluating the spread of ^{224}Ra progeny (^{212}Pb) after intratumoral implantation of ^{224}Ra wires in HCT15 tumor model in nude mice. H&E staining shows correlation with necrotic domains (52). D) Gold-coated lanthanide phosphate nanoparticle allowing retention of ^{225}Ac and its daughters (54). E) Heavy-metal chelation effect on ^{213}Bi renal uptake, 24 hours post-injection of ^{225}Ac -radioimmunotherapy. F) Furosemide and chlorothiazide effect on ^{221}Fr and ^{212}Bi renal uptake, 24 hours post-injection of ^{225}Ac -radioimmunotherapy.

Parent	Daughters	Half-life	α decay	Energy α (MeV)	Other emission	Radiochemistry	Free isotope accumulation	Ref.
²¹¹At		7.2 h	42%	5.87		Tin precursor, prosthetic group	Thyroid, stomach, spleen, lung	(15)
	²¹¹ Po	0.52 s	100%	7.45	K X-rays (77-92 keV)			
	²⁰⁷ Bi	38 y			100% EC			
	²⁰⁷ Po	Stable						
²²⁵Ac		9.9 d	100%	5.94		DOTA, DO3A chelator	Liver, bone	(21,56)
	²²¹ Fr	4.9 m	100%	6.45	218 keV γ		Kidneys, urine	
	²¹⁷ At	32.3 ms	> 99.9%	7.20				
	²¹³Bi	45.6 m	2.2%	5.87	492 keV β^- (97.8%); 440 keV γ	CHX-A"-DTPA, DOTA, NETA	Kidneys, urine	(50)
	²¹³ Po	3.72 μ s	100%	8.38				
	²⁰⁹ Tl	2.16 m			660 keV β^- (100%)			
	²⁰⁹ Pb	3.23 h			198 keV β^- (100%)			
	²⁰⁹ Bi	Stable						
²²⁷Th		18.7 d	100%	6.14	50 and 236 keV γ	DOTA, Me-3,2-HOPO	Bone surface	(25)
	²²³Ra	11.4 d	100%	5.71	269 keV γ		Bone surface	(57)
	²¹⁹ Rn	3.96 s	100%	6.82	271 keV γ			
	²¹⁵ Po	1.78 ms	> 99.9%	7.39				
	²¹¹Pb	36.1 m			471 keV β^- (100%); 404 keV γ		Blood, liver, skeleton, kidneys	(58)
	²¹¹Bi	2.14 m	99.7%	6.62	172 keV β^- (0.3%); 351 keV γ		Kidneys, urine	(58)
	²⁰⁷ Tl	4.77 m			492 keV β^- (100%)			
	²⁰⁷ Pb	Stable						
²²⁴Ra		3.63 d	100%	5.69	241 keV γ		Bone surface	(30)
	²²⁰Rn	55.6 s	100%	6.29				
	²¹⁶ Po	0.15 s	100%	6.78				
	²¹²Pb	10.6 h			93.5 keV β^- (100%); 238 and 300 keV γ	TCMC	Blood, liver, skeleton, kidneys	(31,32)
	²¹²Bi	60.6 m	36%	6.05	834 keV β^- (64%); 727 and 1620 keV γ	CHX-A"-DTPA, DOTA, NETA	Kidneys, urine	(32)
	²¹² Po	0.30 μ s	100%	8.78				
	²⁰⁸ Tl	3.1 m			342, 441, 535 and 649 keV β^- (100%); 2614 keV γ			
	²⁰⁸ Pb	Stable						

Table 1. α -emitters of interest (bold red) for radiotherapy together with their decay progeny. Gray highlighted cells represent daughters with redistribution potency. DOTA: 2,2',2'',2'''-(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid; DO3A: 2,2',2'''-(1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate; CHX-A"-DTPA: 2-(p-isothiocyanatobenzyl)-cyclohexyldiethylenetriaminepentaacetic acid; NETA: {4-{2-{(bis-carboxymethylamino)-ethyl}-7-carboxymethyl-[1,4,7]triazonan-1-yl}-acetic acid; TCMC: 1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane.