Journal of Nuclear Medicine, published on January 4, 2024 as doi:10.2967/jnumed.123.266774

Is ^{212}Pb Really Happening? The Post-^{177}Lu/^{225}Ac Blockbuster?

Richard Zimmermann

Chrysalium Consulting, Lalaye, France; MEDraysintell, Louvain-la-Neuve, Belgium; and Oncidium Foundation, Mont-Saint-Guibert, Belgium

Interest in α-emitters for radiotherapeutic applications is on the rise. However, the number of options for α-emitters with midterm industrial availability remains limited. Currently, only ^{225}Ac, ^{212}Pb, and ^{211}At have realistic chances to reach the market within the next 10 y. A review published in 2022 (*1*) extensively describes the history of development of ^{212}Pb and related technologies. Because industrialization processes and realistic production costs are also important criteria, the aim of this editorial is to confirm that, as for ^{225}Ac (*2*), the industry is seriously tackling the challenge of a large-scale supply of ^{212}Pb with a short-term answer. I conducted a survey among different industrial entities claiming their involvement in such development. Surprisingly, more than 15 companies have made progress in ^{212}Pb production, although some of them are still keeping their work confidential.

ALMOST IDEAL PROFILE

^{212}Pb has a half-life of 10.64 h but is a β-emitter. ^{212}Pb decays into ^{212}Bi (half-life, 60.5 min), which is the α-emitter in the further decay sequence, but only at 36% in ^{208}Tl; the other 64% of the decay arm produces ^{212}Po through another β^--emission. ^{212}Po is a pure α-emitter that decays into stable ^{208}Pb in 0.3 μs, whereas ^{208}Tl is both a β^--emitter and a γ-emitter (half-life, 3.06 min), which also leads to stable ^{208}Pb. Indeed, ^{212}Pb also does not show the expected ideal profile, as it needs to be strongly trapped in the cancer cell to keep all the benefits from the α-emission. The high-energy γ-ray emitted by the ^{208}Tl daughter is an identified drawback that can be solved by lowering doses and shielding health care personnel from high-energy γ-rays. On the other hand, the short half-life maximizes the energy deposition in the tumor cell. Compared with ^{225}Ac, this shorter half-life also eliminates the potential issue of storing radioactive waste, indirectly solving the question of a hospital stay and containment of patients' biologic radioactive waste versus ambulatory treatment. For a specific clinical indication, at equal efficacy, any ^{212}Pb-labeled molecule will have the potential to displace any ^{177}Lu- or ^{225}Ac-labeled analog from the market on the basis of the simple marketing advantage of a lower environmental impact from patients.

Received Nov. 5, 2023; revision accepted Dec. 19, 2023.
For correspondence or reprints, contact Richard Zimmermann (richard.zimmermann@chrysalium.com).
Published online Jan. 4, 2024.

DOI: 10.2967/jnumed.123.266774

DEDICATED CHELATING AGENTS

To really benefit from the efficient secondary α-emission of the radionuclide, the first decay radionuclide, ^{212}Bi, needs to stay trapped within the original lead-atom chelating agent. Significant improvements have been made in this area, and several groups have developed chelating agents that also strongly keep ^{212}Bi attached to the vector (*1*). Since the first emission is a β-emission, the recoil effect that could eject the decay metal out of the chelating cage remains limited and is in no way comparable to the recoil effect of the emission of an α-particle, for which such trapping remains close to impossible.

AN ALTERNATIVE TO COCKTAIL THERAPIES

The evolution of radiotherapeutics is expected to follow the same trend as chemotherapeutics given as cocktails—that is, use of mixtures of radiotherapeutics instead of consecutive treatments—and has already been explored with tandem therapies (mixtures of ^{177}Lu and ^{225}Ac similars). Obviously, the evolution of therapies will combine molecules labeled with different energies of β-emitters and α-emitters or even Auger/conversion electron–emitting radionuclides. By maintaining both the β-emitter and the α-emitter in or next to the cancer cell, the use of ^{212}Pb brings an additional advantage over mixtures with simultaneous efficacy in larger tumors and micrometastases. The ^{212}Pb β-particle contribution has already been proven to be nonnegligible (*3*), and this effect could lead to a reduction in both the doses and their number.

IMAGING WITH LEAD

Quantitative SPECT/CT imaging of ^{212}Pb proved feasible (*4*) but will probably remain used only for development purposes. ^{203}Pb, a γ-emitter with a half-life of 51.87 h, has been presented as the ideal ^{212}Pb surrogate for imaging. However, cyclotron production of ^{203}Pb may not receive industry favor because it would require the creation of a large and expensive network of dedicated tools for access (*5*). Certainly, in the same way as for ^{177}Lu-labeled therapeutic agents, imaging agents used for patient selection will be based on radiodiagnostics labeled with more commonly available radionuclides such as ^{18}F, ^{64}Cu, ^{68}Ga, or ^{99m}Tc.

^{212}PB PRODUCTION ROUTES

Orano Med was the first company to believe strongly in the future of ^{212}Pb and has developed a full production process and started investing in ^{212}Pb-labeled drugs. The company is presently

building 2 industrial facilities called α-therapy laboratories (https://www.oranomed.com/en/industrial-platform) in Indianapolis and Valenciennes with a capacity of 10,000-plus doses per year by 2025 and anticipating more than 10 times this number by the end of the decade.

^{212}Pb is most easily produced through a generator based on the decay of ^{228}Th (*1*). ^{228}Th has a 1.91-y half-life and decays successively into ^{224}Ra (half-life, 3.66 d), ^{220}Rn (56 s), and ^{216}Po (0.14 s), eventually leading to ^{212}Pb through α-emissions in each step. Generators can be based on 3 different processes.

In the first process, ^{212}Pb can be extracted directly from the ^{228}Th decay solution, but this process is the most cumbersome, as it involves handling of the long–half-life ^{228}Th and can therefore be used only in an industrial environment. The first players (Orano Med [France] and TRIUMF [Canada]) originally used this technology but later gave preference to the 2-step processes. Orano Med opted to keep control of the overall process from the production and isolation of thorium to the final radiolabeling and distribution of drugs and therefore does not intend to sell generators. ATOX (Japan), Oncoinvent (Norway), and the Kurchatov Institute (Russia) are also exploring this route.

The second of the 3 processes utilizes the fact that in the decay sequence of ^{228}Th, ^{224}Ra can easily be extracted for loading of ^{224}Ra/^{212}Pb generators. Major players (Perspective Therapeutics [United States], United Well [China], and Pacific Northwest National Laboratory [United States]) use this technology now because generators containing shorter–half-life parent radionuclides will be easier to distribute from a regulatory point of view.

The third process utilizes ^{220}Rn, a gas that can easily be separated from the ^{228}Th/^{224}Ra mixture as soon as it is generated and then left to decay into ^{212}Pb in a second container (*6*). The companies AdvanCell (Australia), AlphaGen Therapeutics (China), ARTBIO (United States), NRG-PALLAS, FutureChemistry (The Netherlands), and Oncoinvent are developing industrial processes based on this technology. ARTBIO claims that its manufacturing approach is poised to scale comfortably to deliver 20,000-plus doses per year once its first program reaches the commercial stage.

^{212}Pb could also be produced directly, without a generator, by using the precursor ^{226}Ra. The conversion reaction in the same tools as those developed for the production of ^{225}Ac or ^{67}Cu (linear accelerator or Rhodotron [IBA Industrial Solutions]) can lead to large amounts of ^{212}Pb, on the basis of the reaction [^{226}Ra(γ,2n)^{224}Ra→^{212}Pb]. In the ^{225}Ac production process based on photoconversion, up to 6 times more ^{212}Pb than ^{225}Ac is generated as a by-product and could be separated. Such a separation process would affect the yields in ^{225}Ac and would be useful only locally. No company is presently developing such a separation process.

Investment in central industrial-scale production centers could remain low, in the range of an ^{18}F manufacturing site investment. Because the half-life of ^{212}Pb will allow overnight shipment to a distance of several thousand kilometers, not only could production costs remain low but individual radiopharmaceutical companies could keep control of their production.

ACCESS TO THE PRECURSORS ^{228}TH AND ^{226}RA

^{228}Th is not considered of concern and is presently available from several governmental or private sources supporting access to ^{212}Pb and recovery of parent isotopes from legacy nuclear material (Department of Energy [United States], Eckert & Ziegler [Germany], Orano [France], Rosatom [Russia], and National Nuclear Laboratory [U.K.]). The nongenerator production route needs access to ^{226}Ra, which should not be an issue in the near future, as it is the main starting material for the production of ^{223}Ra and ^{225}Ac (*2*).

Industrial access to ^{212}Pb is not yet ready, but an impressive number of new players have entered this field over the past 3 y, with several of them proposing new alternatives for access to ^{212}Pb. At the same time, several ^{212}Pb molecules are under development (>20 identified), with 7 having already reached the clinical stage (*7*). There is strong optimism that industrial solutions for large-scale production of ^{212}Pb will be in place before 2028, opening an avenue for a radionuclide that could replace ^{225}Ac over the period 2035–2045.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

I thank Simon Puttick (AdvanCell), Conrad Wueller (ARTBIO), Mizuki Nagarekawa (ATOX), James Hill (FutureChemistry), Tim Tinsley (NNL), Nicolas Bozovic (Orano Med), and Bernhard Sixt and Michael Schultz (Perspective Therapeutics) for sharing information about the stage of development in their respective companies.

REFERENCES

1. Kokov KV, Egotov BV, German MN, et al. ^{212}Pb: production approaches and targeted therapies applications. *Pharmaceutics.* 2022;14:189.
2. Zimmermann R. Is actinium really happening? *J Nucl Med.* 2023;64:1516–1518.
3. Lee D, Li M, Bednarz B, Schultz MK. Modeling cell and tumor-metastasis dosimetry with the Particle and Heavy Ion Transport Code System (PHITS) software for targeted alpha-particle radionuclide therapy. *Radiat Res.* 2018;190:236–247.
4. Kvassheim M, Revheim MER, Stokke C. Quantitative SPECT/CT imaging of lead-212: a phantom study. *EJNMMI Phys.* 2022;9:52.
5. McNeil BL, Robertson AKH, Fu W, et al. Production, purification, and radiolabeling of the ^{203}Pb/^{212}Pb theranostic pair. *EJNMMI Radiopharm Chem.* 2021;6:6.
6. Li RG, Stenberg VY, Larsen RH. An experimental generator for production of high-purity ^{212}Pb for use in radiopharmaceuticals. *J Nucl Med.* 2023;64:173–176.
7. Goethals PE, Zimmermann R. *Nuclear Medicine Report and Directory.* 10th ed. MEDraysintell; September 2023.