Beyond Surrogate Isotopes: Direct Preclinical Imaging of ^{212}Pb with High-Sensitivity VECTor/CT

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What is theranostics, and why is TAT promising?

Theranostics combines diagnostic imaging and targeted radionuclide therapy in a single radiopharmaceutical concept, enabling patient-specific selection, planning, and monitoring of treatment. In oncology, targeted alpha therapy (TAT) has attracted particular interest because α-particles deposit a very high dose over a few cell diameters, due to its high linear energy transfer (LET), potentially eradicating micro-metastatic and treating heterogeneous disease while sparing surrounding normal tissue [1].

Why is ^{212}Pb promising? Its half-life, daughters, and biological half-life.

Among emerging TAT nuclides, lead-212 (^{212}Pb) is especially attractive. 212Pb is a β^--emitter ($T_{1/2} \approx 10.64$ h) that decays to the α-emitter bismuth-212 (^{212}Bi) and, via its short-lived daughters polonium-212 (^{212}Po) and thallium-208 (^{208}Tl), delivers one high-energy α-particle per ^{212}Pb decay within its decay chain [1]. Its half-life is long enough for radiolabeling and biological targeting, but short enough to deliver therapy and clear from the body within 1–2 days, well-suited to peptides and smaller antibodies.

Why is the ^{212}Pb/^{203}Pb pair popular?

A key advantage of ^{212}Pb is its element-matched diagnostic pair lead-203 (^{203}Pb). ^{203}Pb ($T_{1/2} \approx 51.9$ h) is a pure electron-capture radionuclide that emits a 279 keV (~81%) γ-photon suitable for quantitative SPECT imaging [2]. Because ^{203}Pb and ^{212}Pb are isotopes of the same element, radiopharmaceuticals labeled with either isotope share identical coordination chemistry and have a similar in vivo behavior to the parent radioligand. This makes ^{203}Pb/^{212}Pb a compelling theranostic pair: ^{203}Pb for pre-therapy imaging and dosimetry, ^{212}Pb for targeted alpha radiotherapy [3]. However, ^{203}Pb imaging cannot directly capture the potential redistribution of α-emitting daughters in the case of chelator dissociation [4].

Why can ^{212}Pb be considered a good theranostic isotope?

To help address this, ^{212}Pb itself emits several γ-photons (notably 239 keV (~44%) and 75–90 keV X-rays (~36%) from ^{212}Pb, and 583 keV (~85%) from its daughter ^{208}Tl) that can be exploited for SPECT/CT, enabling direct visualization of the therapeutic isotope, although with more challenging image quantification than with ^{203}Pb [2].

Production and availability of ^{212}Pb and ^{203}Pb. What are the limitations?

For any theranostic radionuclide, its clinical impact is ultimately limited by how reliably it can be supplied, and ^{212}Pb and ^{203}Pb have very different production routes with different practical challenges. ^{212}Pb is typically obtained from ^{224}Ra/^{212}Pb or ^{228}Th/^{212}Pb generators, enabling on-site elution and labeling. Automated or cassette-based systems have been developed to provide clinical-grade ^{212}Pb with high specific activity [5]. In contrast, ^{203}Pb is produced on medical cyclotrons (e.g., via proton irradiation of thallium targets), and automated cGMP-

compliant production lines for [^{203}Pb/^{212}Pb]Pb-labeling have now been described [6]. Despite these different supply chains, both isotopes form stable complexes with macrocyclic chelators such as TCMC, DOTA and modified DOTA-like scaffolds, supporting robust labelling of peptides, small molecules or antibodies and thereby limiting off-target toxicity while ensuring effective tumor dose delivery [7].

How MILabs system support imaging of ^{212}Pb in a preclinical set-up?

Imaging ^{212}Pb in small animals is intrinsically demanding. To avoid toxicity from α-emitters, preclinical targeted alpha therapy studies typically use injected activities well below 2 MBq per mouse [8,9]. Such low administered activities, combined with the half-life of ^{212}Pb and the presence of high-energy daughter emissions, can lead to low count statistics and substantial scatter, making quantitative ^{212}Pb SPECT particularly challenging.

The MILabs VECTor/CT system is designed to mitigate these limitations by combining high-sensitivity stationary detectors with a dedicated high-energy ultra-high-sensitivity mouse collimator (HE-XUHS-M-SC). This supercluster-type multi-pinhole collimator reaches system sensitivities on the order of 10–15 % for SPECT (and 17% for PET) and efficiently collimates photons from ~20 keV up to >1 MeV, matching both the 75–90 keV X-rays and the 239 keV γ-ray used for ^{212}Pb imaging.

Phantom evidence: ^{212}Pb imaging

In a quantitative phantom study, a mouse phantom was imaged on both clinical and preclinical SPECT/CT systems. Four ~300 µL volumes filled with 246–303 kBq/mL of ^{212}Pb were distinguishable on the clinical scanner only with aggressive reconstruction settings. The same volumes were clearly resolved on a VECTor/CT system at activity concentrations as low as ~49 kBq/mL. As expected for a dedicated preclinical multi-pinhole SPECT/CT system optimized for small-animal imaging, the VECTor/CT provides substantially higher spatial resolution and better detectability for small ^{212}Pb distributions than a general-purpose clinical SPECT/CT camera under the same phantom conditions (Figure 1) [9]. These observations are consistent with recent ^{203}Pb/^{212}Pb dosimetry and imaging guidelines, which emphasize the use of high-energy collimation and carefully selected 79/239 keV energy windows to balance sensitivity, dead-time and scatter for ^{212}Pb imaging [10].

In vivo evidence: ^{212}Pb imaging

In practice, the combination of high-sensitivity detectors and the high-sensitivity pinhole collimator enables preclinical ^{212}Pb SPECT/CT at the low injected activities typically used in vivo (~0.2–1.5 MBq per mouse), while still providing sufficient count statistics for whole-body biodistribution and tumor imaging within clinically realistic uptake ranges [7,8,11]. An example ^{212}Pb SPECT/CT scan in a mouse is shown in Figure 2. This high sensitivity can be traded either for lower injected activity, reducing renal and

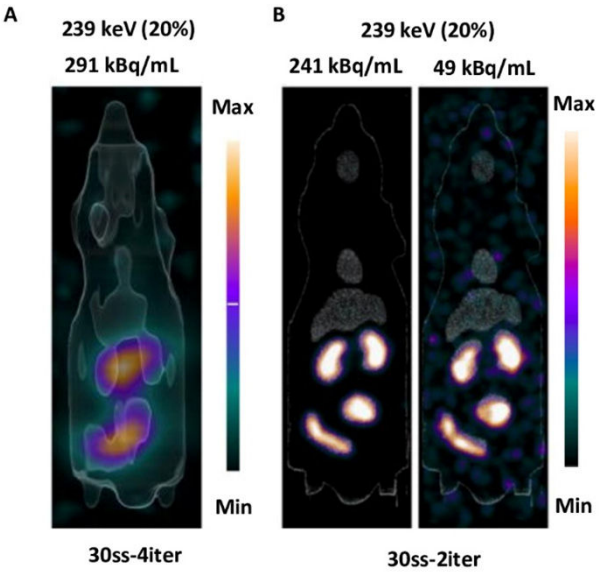

Figure 1. Maximum intensity projection images of the mouse phantom acquired with: (**A**) **Clinical** SPECT/CT scan using a middle energy collimator, image shows the highest activity concentration imaged, 291 kBq/ml of ^{212}Pb in the high-activity concentration volumes. (**B**) **Preclinical** SPECT/CT scan using a middle energy collimator (XX-UHS-M), image shows the highest activity concentration imaged, 241 kBq/ml of ^{212}Pb, similar to the activity concentration when the phantom was imaged on the clinical SPECT but with higher resolution and a later time point with only 49 kBq/ml of ^{212}Pb still clearly showing the four individual filled regions [9].

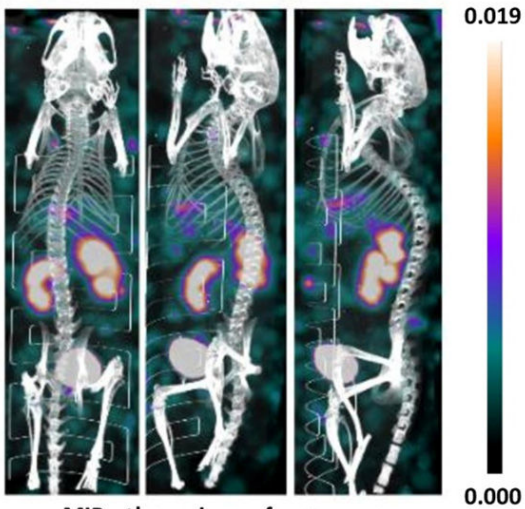

Figure 2. Maximum intensity projections (MIPs) of a mouse intracardially (IC) injected with 2.5 × 10^6 PC-3 PIP-luc cells on day −7 and treated with [^{212}Pb]Pb-AB001 on day 0. Preclinical SPECT/CT imaging (15 min scan with HE-UHS-M collimator) was performed on day 0, 1 h post intravenous administration of 1.0 MBq [^{212}Pb]Pb-AB001, and is shown here from three different viewing angles to illustrate tracer biodistribution [11].

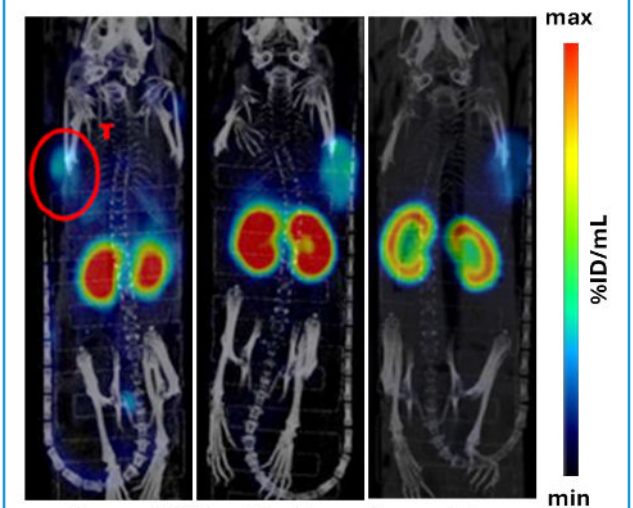

Figure 3. SPECT/CT scans of H69 tumor-bearing mice (n = 4) at 1, 4, and 24 h after the administration of [^{203}Pb]Pb-eSOMA-02. Tumors were located on the right or left shoulder (red **T**). Tumor uptake is expressed as a percentage of injected dose per mL (%ID/mL) [7].

systemic toxicity in α-therapy studies [7,8], or for shorter acquisition times, which improves animal welfare and facilitates longitudinal imaging at multiple time points post-injection.

Evidence of ^{203}Pb as theranostic partner

Because the same VECTor/CT platform can also image the ^{203}Pb surrogate using optimized acquisition protocols, it supports a coherent theranostic workflow: ^{203}Pb for quantitative pre-therapy imaging and dosimetry (Figure 3), and ^{212}Pb for therapy with optional post-therapy verification on the same system [7,8].

Conclusion

Altogether, these studies show that the MILabs VECTor/CT not only performs quantitative ^{203}Pb imaging for dosimetry, but is also sensitive enough to visualize in vivo ^{212}Pb distributions at typical preclinical activities. This capability allows researchers to confirm therapeutic uptake with a single ^{212}Pb administration, without necessarily adding a separate ^{203}Pb imaging dose (e.g. to avoid re-injecting fragile animals or adding extra radiation dose).

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