



Advancing preclinical imaging of α -emitting theranostics

In vivo SPECT visualization of ^{225}Ac -labelled compounds using a high-sensitivity collimator

Sofia Koustoulidou¹, Ruud Ramakers¹⁻², Addison Hunt¹, Chris Kamphuis¹, Justin Jeffery³, Brendan Vastenhout¹

¹ MiLabs B.V., Houten, the Netherlands

² Radiation Detection and Medical Imaging, Delft University of Technology, Delft, the Netherlands

³ Wisconsin Institute for Medical Research, USA

Correspondence: applicationsupport@milabs.com

Overview

Targeted alpha therapy is gaining increasing attention in theranostics, yet preclinical imaging of alpha (α)-emitting radiopharmaceuticals remains challenging due to the low administered activities and complex decay chains associated with these radionuclides. Here, we demonstrate *in vivo* SPECT imaging of ^{225}Ac -labelled compounds in tumour-bearing mice using an ultra-high-sensitivity super-cluster collimator (HE-XUHS-M-SC).

The system enables detection of low kBq activity levels while preserving small-animal spatial resolution. These capabilities may facilitate quantitative biodistribution and dosimetry studies, supporting the translation of preclinical imaging data into the clinical development of theranostic radionuclides like α -emitting isotopes.

The expanding role of α -emitting radionuclides in theranostics

Theranostics has emerged as a transformative strategy in oncology by integrating molecular imaging and targeted radionuclide therapy within a single biologically driven treatment paradigm. Clinically established radiopharmaceutical pairs such as $^{68}\text{Ga}/^{177}\text{Lu}$ -DOTATATE and $^{68}\text{Ga}/^{177}\text{Lu}$ -PSMA have made the “see-and-treat” paradigm a clinical reality in neuroendocrine tumours and prostate cancer, respectively. However, certain characteristics of these beta (β)-particle therapies may limit their efficacy in tumour settings where highly targeted tumour destruction is required.¹

In this context, targeted alpha therapy has emerged as a promising alternative. Radionuclides such as ^{211}At , ^{212}Pb , and ^{225}Ac emit α -particles with high linear energy transfer and a short path length, enabling highly localized tumour cell killing while limiting damage to surrounding tissues.^{1,2} These properties make α -emitting radiopharmaceuticals particularly promising for treating minimal residual and micrometastatic disease, where conventional β -particle therapies may be less effective.³ While an increasing number of α -emitting radiopharmaceuticals are entering clinical trials, preclinical studies focus on identifying optimal combinations of molecular targets, targeting vectors, and radionuclides.^{3,4}

Preclinical imaging challenges for the translational development of α -emitting radiopharmaceuticals

Accurate characterization of *in vivo* biodistribution, pharmacokinetics, and radiation dose delivery in physiologically relevant tumour models is essential for translational decision-making.^{4,5} However, preclinical studies of α -emitting radiopharmaceuticals are constrained by several practical factors. Translationally relevant experiments with radionuclides such as ^{225}Ac require extremely low administered activities.

In addition, their complex decay chains generate daughter radionuclides, including ^{221}Fr and ^{213}Bi , which may redistribute to non-target tissues and complicate the interpretation of biodistribution and dosimetry measurements.⁶ Under these conditions, the number of detectable photons on conventional preclinical SPECT systems is frequently insufficient for robust quantitative imaging at relevant activity levels.^{6,7} Consequently, studies often rely on sparse imaging schedules or *ex vivo* biodistribution measurements, which can obscure dynamic pharmacokinetics and reduce the translational value of preclinical datasets.^{4,6}

Advancing sensitivity in preclinical SPECT imaging of α -emitters

Imaging systems with substantially higher sensitivity are required to enable quantitative visualization of α -emitter biodistribution at clinically relevant activity levels.^{4,6} Advances in high-sensitivity preclinical SPECT imaging have enabled improved spatial, temporal, and energy resolution across a wide photon-energy range, allowing simultaneous imaging of multiple radionuclides in theranostic experiments.⁸ A super-cluster collimator, implemented on the VECTor imaging platform (MILabs, the Netherlands), provides ultra-high sensitivity (~17 %) while maintaining a spatial resolution of approximately 1.1 mm.

To evaluate the imaging performance of the system for ^{225}Ac , phantom and *in vivo* imaging experiments were performed (Figure 1).

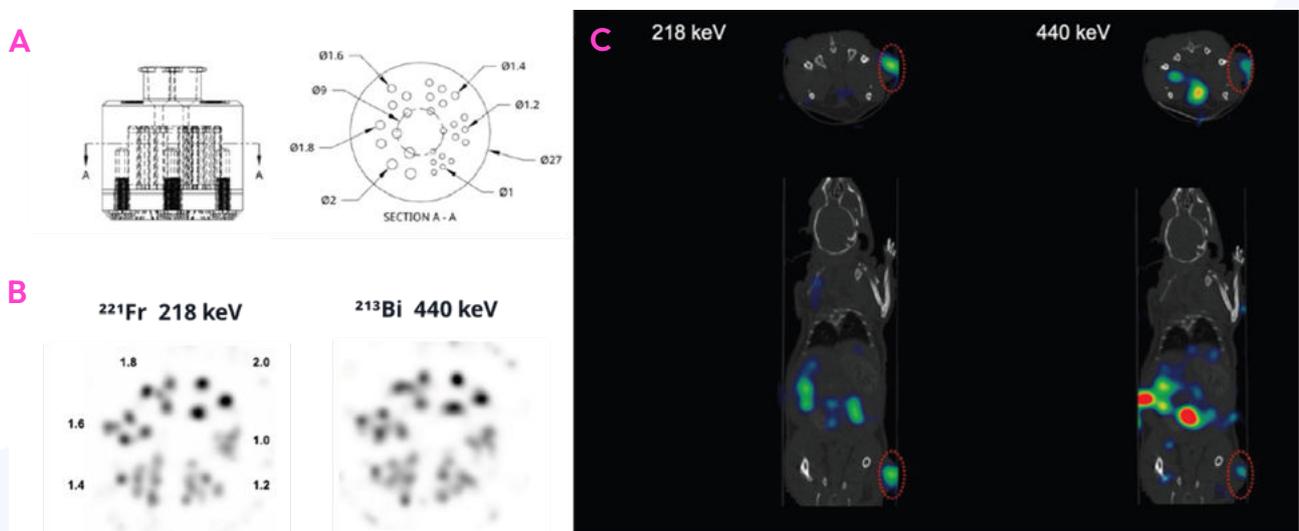


Figure 1. High-sensitivity imaging of ^{225}Ac -labelled compounds using the super-cluster collimator.

- A)** Schematic representation of the hot-rod phantom containing rods ranging from 1.0 to 2.0 mm in diameter.
B) Resolution phantom imaging of ^{225}Ac , using the 218 keV and 440 keV photopeaks corresponding to the daughter radionuclides ^{221}Fr and ^{213}Bi in the ^{225}Ac decay chain.
C) *In vivo* SPECT/CT imaging of tumour-bearing mice injected with 74 kBq of ^{225}Ac -labelled targeting ligand showing detectable tumour uptake for both the 218 keV and 440 keV photopeaks, 24 hours post-injection.

Phantom imaging demonstrated spatial resolutions of approximately 1.4 mm and 1.6 mm for the 218 keV and 440 keV photopeaks, respectively (Figure 1A–B). *In vivo* SPECT/CT imaging of tumour-bearing mice injected with 74 kBq of ^{225}Ac -labelled targeting ligand showed detectable tumour uptake for both photopeaks 24 hours post-injection (Figure 1C). Differences between the two energy windows were observed: 218 keV images showed more prominent kidney uptake, whereas 440 keV images revealed more pronounced intestinal signal.

Methods

Phantom imaging

A hot-rod phantom (Phantech, Madison, WI, USA) containing rods ranging from 1.0 to 2.0 mm in diameter was filled with 270 kBq of ^{225}Ac and scanned using spiral scan mode with a total acquisition time of 3 hours.

In vivo imaging

Tumour-bearing mice were injected with 74 kBq of ^{225}Ac -labelled targeting ligand and imaged for 50 minutes, 24 hours post-injection, using preclinical high-energy SPECT/CT (MILabs, the Netherlands). All animal experiments were conducted under approved institutional protocols.

Image reconstruction

Images were reconstructed for two separate photopeaks representing ^{221}Fr and ^{213}Bi using the SROSEM algorithm (MILabs, the Netherlands) with 0.8 mm voxel size and 4.4 mm Gaussian filtering. Visualization was performed using PMOD software (version 4.4; PMOD Technologies, Bruker).

Implications for preclinical imaging of α -emitting theranostics

To our knowledge, this study demonstrates the first in vivo imaging of ^{225}Ac -labelled compounds in live animals using a preclinical SPECT scanner, with clear visualization at high photon energies. The enhanced sensitivity of the super-cluster collimator enables imaging of small injected activities in the kBq-per-mouse range, consistent with realistic therapeutic ^{225}Ac dosing in preclinical studies.^{9,10}

The ability to resolve multiple photopeaks within the ^{225}Ac decay chain enables multi-energy imaging approaches that may support dynamic studies of ^{225}Ac biodistribution and daughter radionuclide behaviour, potentially reducing reliance on sparse imaging time points and ex vivo tissue counting. Importantly, this level of sensitivity is achieved without compromising lesion-scale spatial resolution, which may support quantitative volume-of-interest-based pharmacokinetic analysis and organ-level dosimetry.

At the preclinical level, most imaging studies of ^{225}Ac and other α -emitters have relied either on conventional small-animal SPECT systems with limited sensitivity at high photon energies or on experimental coded-aperture, Compton, or collimator-less detector approaches, which provide higher sensitivity but relatively coarse spatial resolution at the multi-millimetre scale.^{7,11}

By combining high sensitivity with true small-animal spatial resolution, the super-cluster collimator opens new possibilities for quantitative biodistribution and dosimetry studies, supporting the translation of α -emitting theranostics toward clinical development.

References

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