Advancing preclinical imaging of α-emitting theranostics

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

Sofia Koustoulidou[1], Ruud Ramakers[1-2], Addison Hunt[1], Chris Kamphuis[1], Justin Jeffery[3], Zerguit Adnane[4], Sunay Rodriguez Pérez[4], Brendan Vastenhouw[1]

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
4 Research in Dosimetric Applications - RadioPharma Research – Nuclear Medical Applications Institute, Belgium

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}Ga/^{177}Lu-DOTATATE and ^{68}Ga/^{177}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). 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 *in vivo* SPECT/CT imaging of tumour-bearing mice injected with 94 kBq of ^{225}Ac-PSMA I&T (Figure 1C), tumor uptake was visible as early as 4 hours post-injection, peaking at 24 and 48 hours. In contrast, kidney uptake was pronounced at 1, 4, and 24 hours p.i., followed by complete clearance at 48 hours p.i..

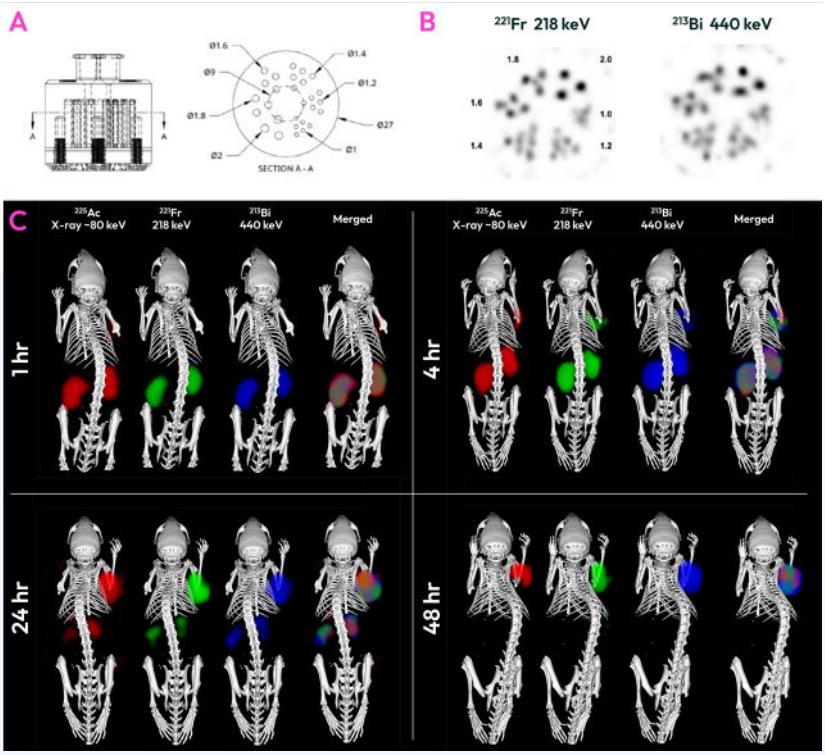

Figure 1. High-sensitivity imaging of ^{225}Ac-labelled compounds using the super-cluster collimator.
A) Schematic representation of the hot-rod phantom containing rods ranging from 1.0 to 2.0 mm in diameter.
B) Resolution phantom imaging of ^{225}Ac, using the 218 keV and 440 keV photopeaks corresponding 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 94 kBq of ^{225}Ac-PSMA I&T showing detectable tumour uptake for the 80 keV (X-ray), 218 keV and 440 keV photopeaks, 1, 4, 24, and 48 hours post-injection.

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 94 kBq of ^{225}Ac-PSMA I&T and imaged for 60 minutes, 1, 4, 24, and 48 hours p.i., using preclinical high-energy SPECT/CT (MILabs, the Netherlands). All animal experiments were conducted under approved institutional protocols.

Image reconstruction

Images were reconstructed for three separate photopeaks representing X-rays, ^{221}Fr, and ^{213}Bi using the SROSEM algorithm (MILabs, the Netherlands) with 0.6 mm voxel size and 15 iterations. Visualization was performed using Imalytics Preclinical software (version 3.1; Gremse-IT GmbH, Germany).

Implications for preclinical imaging of α-emitting theranostics

This study demonstrates *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.

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