[^{99m}Tc]Tc-3PRGD2: A first-in-class integrin-targeting SPECT tracer expands the clinical landscape of oncologic nuclear medicine

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INTRODUCTION

For nearly three decades, [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) PET/CT has reigned as the gold standard for cancer imaging, guiding critical decisions in cancer management. However, its high costs, logistical complexity, and limited accessibility have left the majority of cancer patients worldwide without access to precision molecular imaging. In contrast, SPECT technology is far more affordable and widely available, and it already boasts a clinically meaningful tracer repertoire of many approved technetium-based radiopharmaceuticals for various indications. Nevertheless, the field has long lacked broadly adopted tumor-targeted SPECT tracers with clinical impact comparable to that of [^{18}F]FDG PET/CT. This gap arises from the absence of molecular tools capable of visualizing cancer with adequate sensitivity and specificity.

On April 2, 2026, a landmark achievement in this field was announced: China's National Medical Products Administration (NMPA) granted market approval to [^{99m}Tc]Tc-3PRGD2, a first-in-class integrin-targeting SPECT radiopharmaceutical developed by Professor Fan Wang's team at Peking University (Figure 1). This agent is an integrin-targeted SPECT radiopharmaceutical developed for oncologic imaging and also China's first Class 1 innovative nuclear diagnostic drug. Its approval finally provides the long-missing tumor-targeted tracer, addressing a long-standing clinical challenge and marking a meaningful advance in the field.

MOLECULAR DESIGN AND MECHANISM: RATIONAL ENGINEERING FOR CLINICAL UTILITY

The success of [^{99m}Tc]Tc-3PRGD2 lies in its sophisticated molecular architecture, which is designed to optimize both biological targeting and clinical workflow. The ^{99m}Tc center is coordinated by a HYNIC-3PRGD2 conjugate (where the bicyclic RGD peptides are linked via a PEG_4-based spacer), along with two coligands: Tricine (tris(hydroxymethyl)methylglycine) and TPPTS (triphenylphosphine-3,3′,3′′-trisulfonic acid trisodium salt) (Figure 1, upper left panel). The PEG_4-based spacer enhances hydrophilicity and pharmacokinetics, while the bicyclic RGD motif confers high-affinity binding to integrin αvβ3, a receptor highly expressed on tumor cells and neo-vasculature. Tricine coordinates to ^{99m}Tc, contributing to the stability of the complex and enabling efficient radiolabeling. TPPTS, bearing three sulfonate groups, further increases hydrophilicity, promoting rapid renal clearance and minimizing nonspecific uptake. Unlike conventional ^{99m}Tc-HYNIC complexes that often require post-labeling purification, this mixed-ligand coordination system ensures exceptionally high stability and radiochemical purity (> 95% without post-labeling purification), enabling the kit-based, on-site preparation that is critical for routine clinical SPECT imaging.

The biological rationale for targeting integrin αvβ3 is well-established. This receptor is selectively upregulated on activated endothelial cells during angiogenesis—the process by which tumors recruit new blood vessels to support growth and metastasis—and is also expressed on many types of tumor cells. By binding to integrin αvβ3, [^{99m}Tc]Tc-3PRGD2 effectively "lights up" both the tumor and its angiogenic vasculature, enabling SPECT to visualize malignant lesions with high contrast (Figure 1, upper right panel).

Preclinical biodistribution studies have confirmed rapid tumor uptake and predominant renal excretion, with minimal brain penetration and low retention in non-target organs. This favorable profile translates clinically into high tumor-to-background ratios, allowing clear delineation of primary tumors and metastatic lesions.

CLINICAL EVIDENCE AND POSITIONING

In a head-to-head clinical trial, [^{99m}Tc]Tc-3PRGD2 performed on par with [^{18}F]FDG PET/CT for differentiating benign from malignant lung lesions (sensitivity, 96% vs 98%, $P = 0.083$), while showing significantly higher specificity (74% vs 50%, $P < 0.001$) and accuracy (70% vs 55%, $P < 0.001$) for lymph node metastasis evaluation, reducing false-positive findings in comparison with PET/CT.[1] Beyond the lungs, robust evidence supports its utility in breast cancer (92.9% sensitivity for neoadjuvant chemotherapy response prediction),[2] esophageal cancer (85.1% accuracy for lymph node staging),[3] and differentiated thyroid cancer (96.6% sensitivity for recurrence monitoring).[4] These striking results demonstrate that an affordable, accessible SPECT agent can achieve diagnostic power comparable to the expensive PET standard—and even surpass it in lymph node evaluation. In this setting, [^{99m}Tc]Tc-3PRGD2 helped reduce false-positive interpretation relative to [^{18}F]FDG PET/CT in a specific clinical context.

How should [^{99m}Tc]Tc-3PRGD2 be positioned in the current oncological imaging landscape? The evidence suggests it is best understood as a highly accessible, cost-effective complement to PET/CT, not a wholesale replacement. Its advantages are clear: SPECT scanners are already widely deployed, including in county-level hospitals in China; kit-based on-site preparation requires only 30 minutes; and the total cost is substantially lower than that of PET/CT, making repeat imaging for treatment monitoring economically feasible. However, several limitations must be frankly acknowledged—a hallmark of responsible academic commentary. The strongest Phase III data currently pertain to thoracic lesions, particularly lung cancer, while formal regulatory approval for breast, esophageal, and thyroid cancers will require additional trials. SPECT inherently offers lower spatial resolution than PET, making it less suitable for lesions smaller than 5–8 mm. Furthermore, as [^{99m}Tc]Tc-3PRGD2 enters broad clinical use, establishing standardized imaging protocols across different centers will be essential to ensure consistent performance.

STRATEGIC OUTLOOK

The approval of [^{99m}Tc]Tc-3PRGD2 marks a significant milestone, yet it is far from the endpoint. Looking ahead, two strategic directions emerge from this achievement. First, future direction in theranostic development: the same integrin αvβ3-targeting principle can be extended therapeutically. Professor Wang's team has advanced [^{177}Lu]Lu-AB-3PRGD2—a lutetium-177-labeled therapeutic analog—into clinical development, with a first-in-human study already demonstrating promising efficacy and a manageable safety profile.[5] This "theranostic pair" ([^{99m}Tc]Tc for diagnosis, [^{177}Lu]Lu for therapy) exemplifies the future of personalized oncology: *see what you treat, and treat what you see* (Figure 1, lower left panel). Patients who show strong tumor uptake on [^{99m}Tc]Tc-3PRGD2 SPECT could be candidates for future theranostic assessment with [^{177}Lu]Lu-AB-3PRGD2 radionuclide therapy, potentially benefiting millions with advanced or metastatic disease. Second, supporting broader clinical availability and contributing to more equitable access to imaging sevives: China's national "One County, One Nuclear Medicine Depart-

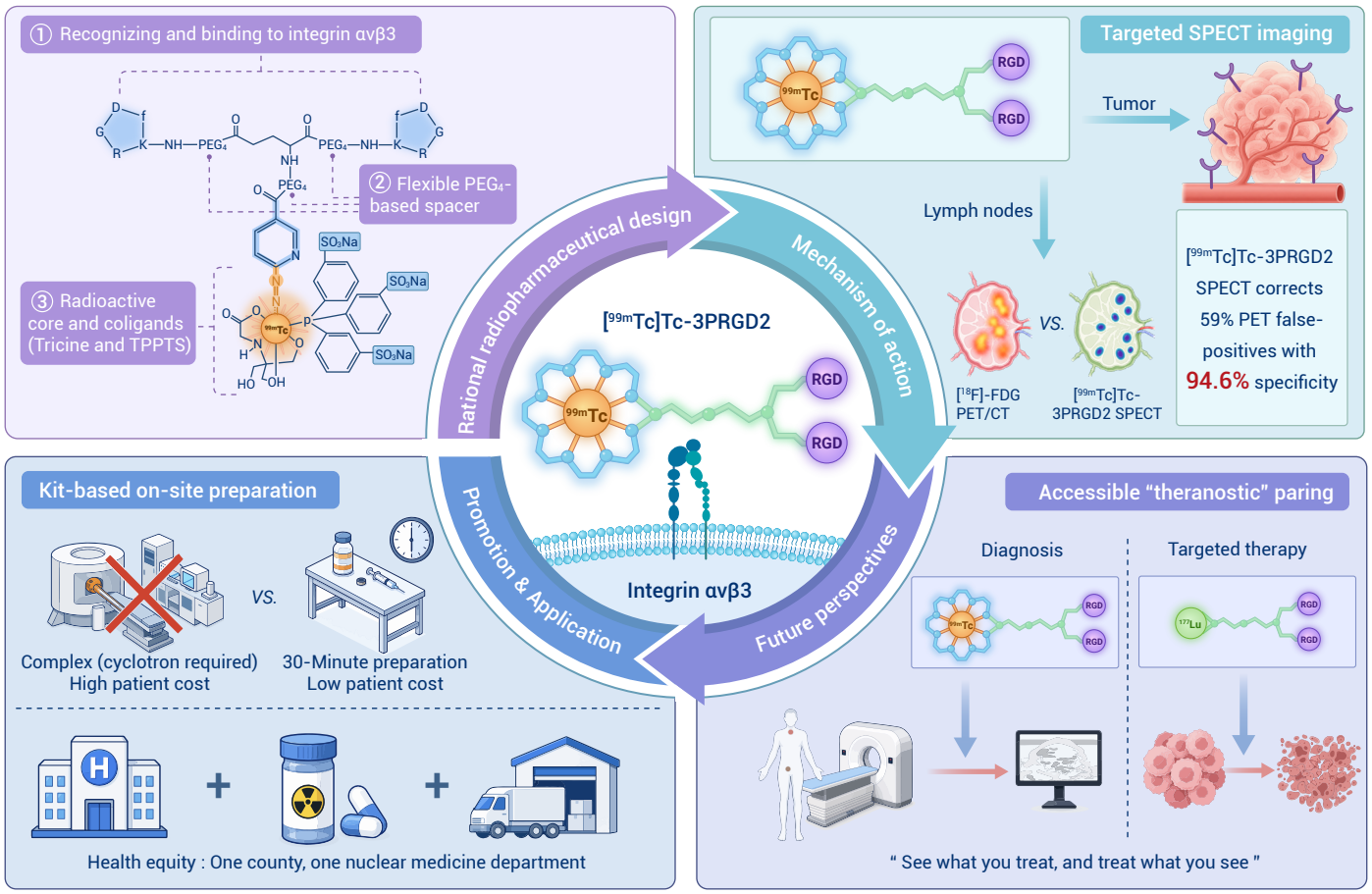

Figure 1. Schematic illustration of [^{99m}Tc]Tc-3PRGD2: from coordination chemistry to clinical advantages

ment" initiative (2021–2035) aims to bring nuclear medicine services to all county-level hospitals (Figure 1, lower right panel). By enabling high-quality tumor imaging on existing SPECT scanners at low cost, [^{99m}Tc]Tc-3PRGD2 can help extend precision imaging services to resource-limited settings, allowing patients in rural areas to receive accurate staging without traveling to major metropolitan centers. However, realizing this vision also hinges on a resilient supply chain. The global nuclear medicine supply chain remains fragile, concentrated around a few aging research reactors. Recognizing this vulnerability, China has made strategic investments in domestic ^{99}Mo production, including both accelerator-based and reactor-based methods. Accelerating these efforts is essential to ensure that the clinical adoption of [^{99m}Tc]Tc-3PRGD2 is not constrained by dependence on isotope imports.

CONCLUSION

[^{99m}Tc]Tc-3PRGD2 represents an important step forward in radiopharmaceutical science, proving that affordable, accessible SPECT imaging can achieve—and in some aspects exceed—the diagnostic performance of expensive PET technology. It expands the clinical landscape of oncologic nuclear medicine and establishes a new model for nuclear medicine innovation: one that prioritizes health equity and broad accessibility alongside scientific excellence. For the field of oncology, this means more patients, especially those in underserved regions, may have access to precision molecular imaging. For the field of radiopharmaceutical science, it validates the mixed-ligand, kit-based approach as a platform technology. And for China, it demonstrates the capacity to lead in an area long dominated by Western pharmaceutical giants. As [^{99m}Tc]Tc-3PRGD2 enters clinical practice and its therapeutic partner advances through the pipeline, the vision of "theranostics for all"—precise, affordable, and accessible cancer care—has the potential to come one step closer to reality.

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AUTHOR CONTRIBUTIONS

All authors conceived the original idea, wrote and reviewed the manuscript. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.