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Brief Communication

Multivalent FAPI-based radiopharmaceuticals in PET/CT: from cancer diagnostics to theranostics

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Abstract: Radiopharmaceuticals targeting fibroblast activation protein (FAP) have rapidly emerged as innovative agents for cancer imaging and therapy. By selectively binding to cancer-associated fibroblasts (CAFs), radiolabeled FAP inhibitors (FAPIs) enable high-contrast PET/CT imaging across diverse tumor types. This article highlights recent advances in FAPI PET/CT imaging, with particular focus on the influence of multivalency effect in radiotracer development.

Keywords: Cancer theranostics, fibroblast-activation protein inhibitor (FAPI), positron emission tomography/computed tomography (PET/CT)

Introduction

Positron emission tomography/computed tomography (PET/CT) is a hybrid imaging technology that integrates functional and anatomical imaging to provide comprehensive information in oncology, cardiology, and neurology. PET imaging has revolutionized cancer diagnostics, enabling non-invasive visualization of physiological and pathological processes during clinical evaluations [1-4]. The PET tracer [^{18}F]Fluorodeoxyglucose (FDG), widely used for mapping glucose metabolism, has become indispensable in oncology for tumor detection, staging, and monitoring treatment response [5]. Despite its clinical utility, [^{18}F]FDG is limited to diagnostics, lacks therapeutic applications, and demonstrates some drawbacks, such as non-specific uptake in inflammatory or non-cancerous conditions, which may lead to off-target effects in cancer management [6]. To address these limitations, more specific radiotracers have been developed, including radiolabeled inhibitors of fibroblast activation protein (FAP), a transmembrane glycoprotein found on activated fibroblasts, particularly cancer-associated fibroblasts (CAFs) [7, 8].

Cancer-associated fibroblast in the tumor microenvironment

CAFs, essential component of the tumor microenvironment (TME), play significant roles in promoting tumor growth and malignancy [9]. CAFs are primarily formed through the activation of normal fibroblasts in response to cytokine and chemokine signals from cancer cells. These signals, including growth factor beta (TGF-β) and stromal cell-derived factor 1 (SDF-1), trigger the fibroblasts' transformation into a more aggressive phenotype. Upon activation, CAFs contribute to tumor progression by secreting these signals to facilitate cancer cell proliferation, migration, and invasion, while remodeling the TME to support malignancy. FAP is found at low levels in normal fibroblasts but significantly overexpressed in CAFs [10], which represents a promising target for developing theranostic applications to improve cancer treatment by specifically targeting the tumor microenvironment (**Figure 1**). This advantage is particularly evident in cancers with high fibroblast activation and low glucose metabolism, including pancreatic cancer, cholangiocarcinoma, sarcomas, ovarian cancer, and gastrointestinal stromal tumors (GISTs) [11-14]. Compared to FDG-PET, which struggles with detecting tumors in low-glucose-metabolizing tissues or those with inflammatory uptake interference, FAPI-PET has shown superior tumor delineation and specificity in these malignancies.

Literature highlight

Recently, radiolabeled quinoline-based FAP inhibitors, such as FAPI-04 and FAPI-46, have demonstrated promising potential in diagnosing cancer and other diseases, leading to intensified research efforts in this area. Among these, [^{68}Ga]Ga-FAPI-04 demonstrated remarkably high uptake in several prevalent cancers. Optimization of the linker with an *N*-methyl fragment and diazabicyclo heptane moiety based on FAPI-04, [^{68}Ga]Ga-FAPI-46 showed greater tumor uptake than [^{68}Ga]Ga-FAPI-04 (**Figure 2**). However, a key challenge is that these FAPI tracers have a relatively short tumor retention time, which may limit their therapeutic effectiveness [15].

To further improve tumor uptake and retention, several strategies have been developed mainly based on optimiz-

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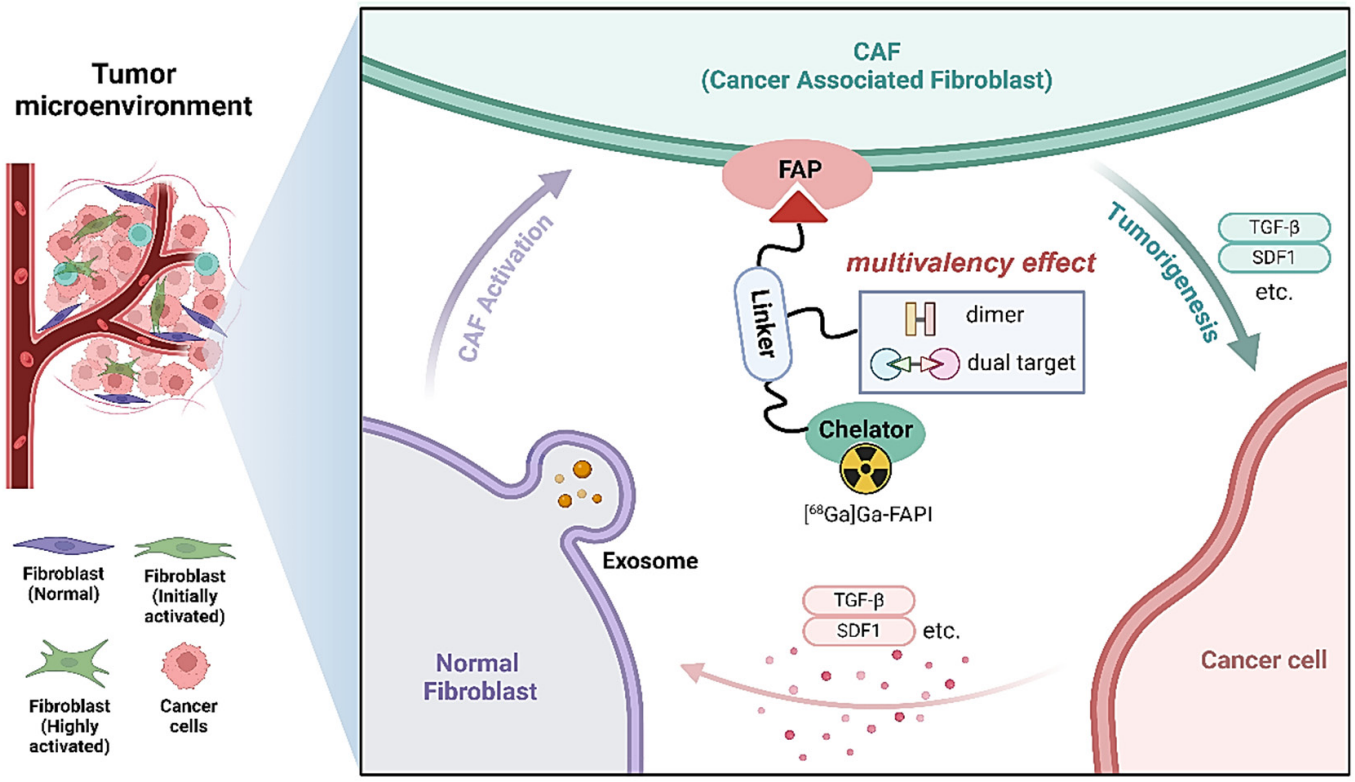

Figure 1. This diagram illustrates the recruitment process of cancer-associated fibroblasts (CAFs) into the tumor microenvironment (TME) and outlines the development strategies for FAPI-based radiotracers.

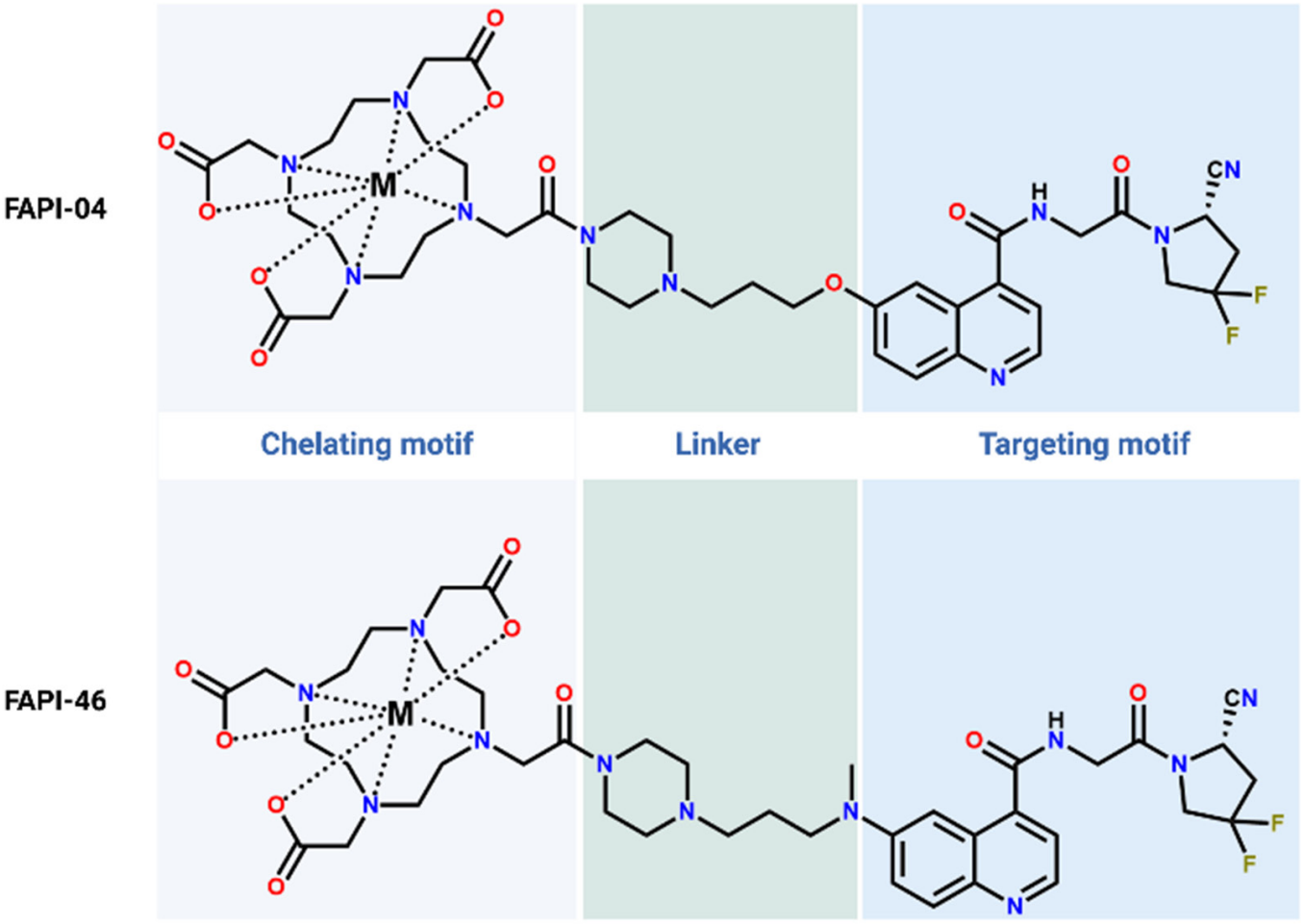

Figure 2. The chemical structure of FAPI-04 and FAPI-46. Both tracers consist of a chelating motif (binding metal radionuclides like ^{68}Ga or ^{177}Lu), a linker, and a targeting motif for FAP binding.

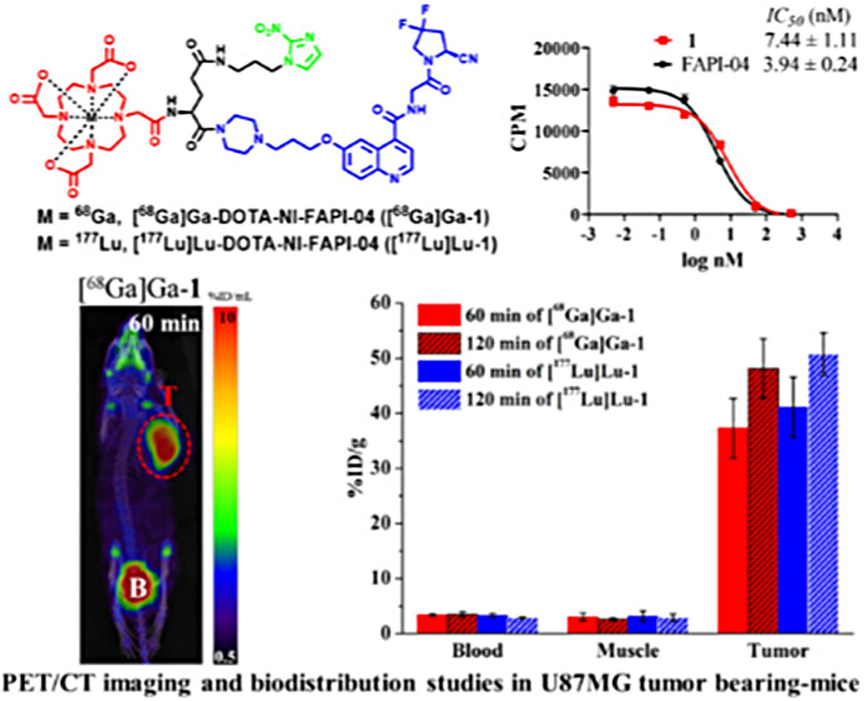

Figure 3. The structure of novel bivalent-targeting FAPI tracers [^{68}Ga]Ga/[^{177}Lu]Lu-DOTA-NI-FAPI-04; The nonradioactive ligand demonstrated high binding affinity; The radiolabeled tracers exhibited enhanced tumor uptake and retention. Reprinted with permission from [17]. Copyright 2024 American Chemical Society.

ing the linker or chelator, introducing multimer or multi-target structures, and utilizing peptides [16]. In this context, Luo et al. designed and synthesized a novel bivalent FAPI tracer, [^{68}Ga]Ga/[^{177}Lu]Lu-DOTA-NI-FAPI-04, by incorporating a hypoxia-sensitive nitroimidazole moiety. The ligand exhibited high affinity for FAP, with an IC_{50} of 7.44 ± 1.11 nM, comparable to the 3.94 ± 0.24 nM observed for FAPI-04 [17]. Radiolabeled tracers [^{68}Ga]Ga-1 and [^{177}Lu]Lu-1 demonstrated enhanced cell uptake in vitro. In vivo PET/CT imaging revealed that [^{68}Ga]Ga-1 exhibited significantly higher specific uptake and retention in U87MG tumor-bearing mice compared to [^{68}Ga]Ga-FAPI-04, enabling superior visualization of both primary tumors and metastatic sites (**Figure 3**).

This study advances the field by introducing an effective strategy to design and optimize FAPI-based radiotracers. By leveraging the multivalency/multi-target effects [18-21], these tracers demonstrated enhanced tumor-specific uptake and retention, improving their potential efficacy in cancer management. Despite these advantages, there are also concerns regarding the higher physiological uptake of [^{68}Ga]Ga-1 and [^{177}Lu]Lu-1 in the blood, muscle, and bone, which could potentially increase the risk of toxicity in these tissues.

Another notable advancement in FAPI-based radiopharmaceuticals is [^{177}Lu]Lu-OncoFAP-23, a homotrimeric FAP-targeting ligand engineered to enhance tumor uptake and retention (**Figure 4**). The trimerization of OncoFAP significantly increases FAP binding affinity - approximately 35-fold higher than its monovalent counterpart - thereby improving tumor localization and reducing renal clearance. Preclinical biodistribution studies have demonstrated that [^{177}Lu]Lu-OncoFAP-23 exhibits prolonged tumor retention with reduced off-target accumulation, addressing a key limitation of earlier FAPI tracers. Furthermore, tumor growth inhibition studies have substantiated its superior therapeutic efficacy, with [^{177}Lu]Lu-OncoFAP-23 achieving greater tumor volume reduction than monovalent [^{177}Lu]Lu-OncoFAP. These findings underscore the potential of multivalent ligand design in optimizing FAPI-based radiopharmaceuticals for both diagnostic and therapeutic applications, offering a promising avenue for improving radioligand therapy outcomes [22].

Outlook of FAPI radiopharmaceuticals

Undoubtedly, FAPI-based radiopharmaceuticals have become a rapidly evolving field of research, demonstrating significant diagnostic and/or therapeutic potential for clinical applications. Moving forward, the development of FAPI radiopharmaceuticals will necessitate a careful balance among selecting binding moiety, optimizing linker structures and selecting appropriate radionuclides. Furthermore, the potential of FAPI-based PET tracers extends far beyond lesion detection. These tracers are widely regarded as invaluable tools for identifying cancer patients eligible for FAP-targeted radionuclide therapy and for quantitative, noninvasive monitoring treatment responses. However, current FAPI radiotracers have yet to fully meet expectations in preclinical and clinical studies. A primary limitation is their relatively short tumor retention time, which results from factors such as rapid clearance and metabolism, ultimately reducing drug accumulation at tumor sites. This diminishes therapeutic efficacy by delivering insufficient radiation doses to tumors and increases the risk of unnecessary radiation exposure to healthy tissues due to rapid clearance. Therefore, the development of more effective tracers with enhanced tumor uptake and retention is urgently needed. Such

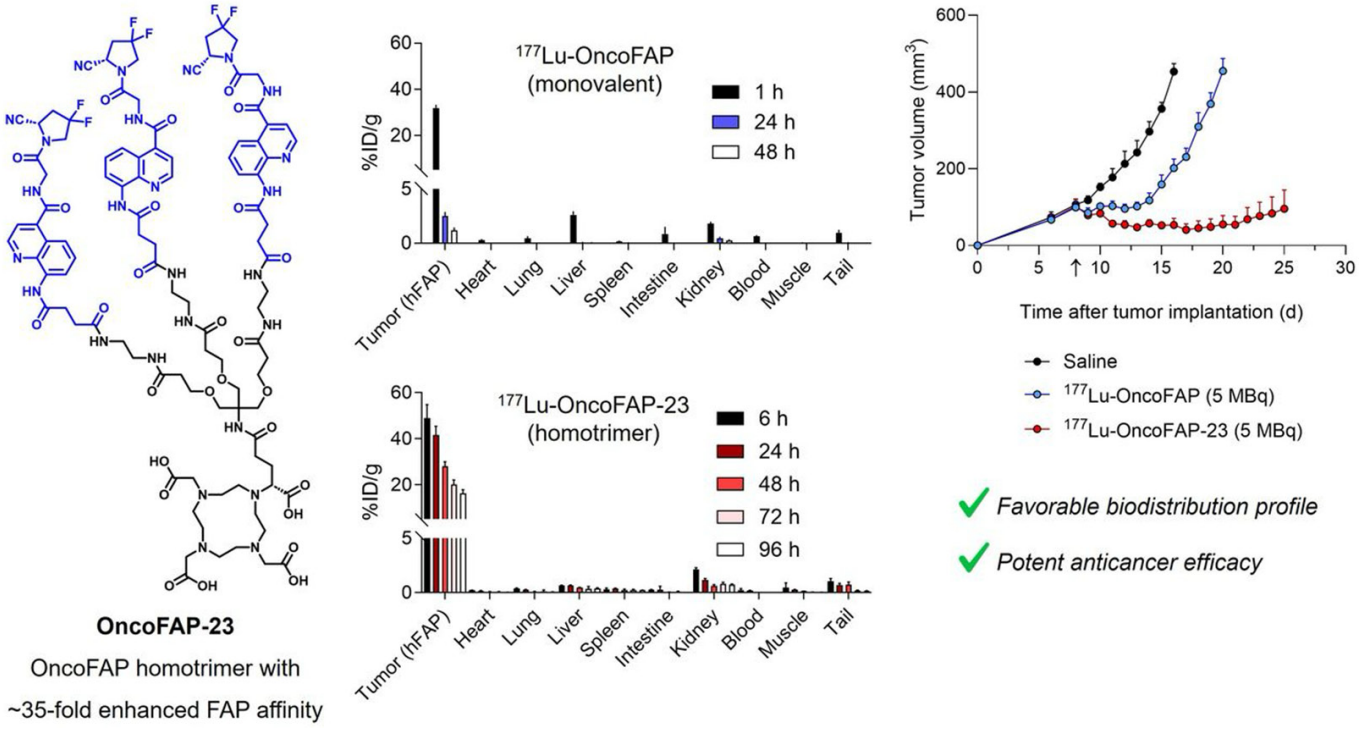

Figure 4. Enhanced tumor targeting and therapeutic efficacy of [^{177}Lu]Lu-OncoFAP-23. The homotrimeric structure of OncoFAP-23 improves FAP affinity, tumor retention, and biodistribution, leading to superior anticancer efficacy compared to its monovalent counterpart. Reprinted with permission from [22]. Copyright 2024 Society of Nuclear Medicine and Molecular Imaging (SNMMI).

advancements are essential to fully realize the theranostics potential of FAPI-based radiopharmaceuticals.

Disclosure of conflict of interest

None.

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