FAPI-BASED RADIOPHARMACEUTICALS IN MODERN THERANOSTICS: FROM DIAGNOSTIC IMAGING TO TARGETED RADIONUCLIDE THERAPY

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Abstract

Fibroblast activation protein inhibitor (FAPI)-based radiopharmaceuticals have emerged as one of the most promising innovations in contemporary nuclear medicine and precision oncology. Fibroblast activation protein (FAP), overexpressed in cancer-associated fibroblasts (CAFs) within the tumor microenvironment of many epithelial malignancies, has become an important molecular target for both diagnostic imaging and targeted radionuclide therapy. In recent years, FAPI radiopharmaceuticals have demonstrated outstanding diagnostic performance characterized by rapid tumor uptake, low physiological accumulation in healthy tissues, and excellent tumor-to-background contrast in positron emission tomography/computed tomography (PET/CT) imaging. Furthermore, therapeutic radionuclides such as Lutetium-177, and Actinium-225 have enabled the development of FAPI-based radionuclide therapy, expanding the role of FAPI compounds from diagnostic imaging to therapeutic oncology. This review discusses the biological basis of FAP targeting, the development and radiochemistry of FAPI radiopharmaceuticals and their current clinical applications in diagnostic imaging and targeted radionuclide therapy. Among other aspects, we aimed to highlight the major limitations, current challenges, and future perspectives of FAPI theranostics in precision medicine.

Keywords: FAPI, fibroblast activation protein, theranostics, PET/CT imaging, targeted radionuclide therapy, radiopharmaceuticals.

Introduction

Theranostics has become one of the most rapidly developing concepts in modern radiopharmacy andnuclear medicine, combining molecular imaging and targeted therapy into a unified personalized treatment strategy. Among the emerging theranostic agents, fibroblast activation protein inhibitor (FAPI)-based radiopharmaceuticals have attracted significant scientific and clinical interest because of their ability to target fibroblast activation protein (FAP), a membrane-bound serine protease highly expressed on cancer-associated fibroblasts (CAFs) within the tumor microenvironment of many epithelial malignancies (Siegmund SC et al., 2025). Unlike conventional radiopharmaceuticals that primarily target tumor cell metabolism, FAPI radiopharmaceuticals focus on the tumor stroma, which plays a critical role in tumor growth, invasion, angiogenesis, metastasis, and resistance to therapy (Huang X et al., 2026). Targeting tumor stroma via FAPI represents a promising theranostic approach. Radiopharmaceuticals labeled with diagnostic (99mTc) or therapeutic (177Lu) isotopes enhance imaging specificity and enable targeted therapy (Rustemi-Ahmeti H et al., 2026).
Radiolabeled FAPI compounds, particularly those labeled with Gallium-68 and Fluorine-18, have shown excellent pharmacokinetic characteristics, including rapid tumor uptake, fast blood clearance, and high tumor-to-background ratios, making them highly suitable for PET/CT imaging (Kratochwil C et al., 2019). Clinical studies have demonstrated promising results across multiple malignancies, including pancreatic, breast, lung, colorectal, ovarian, gastric, and head and neck cancers. Moreover, the replacement of diagnostic radionuclides with therapeutic isotopes such as Lutetium-177 and Actinium-225 has enabled the development of

FAPI-based targeted radionuclide therapy, establishing FAPI compounds as important agents in modern theranostics (Wu X et al., 2025). Freeze-dried formulations improve stability, handling, and reproducibility, which are essential for preclinical and clinical translation (Rustemi-Ahmeti H et al., 2026). This technique is widely used in the pharmaceutical industry for the stabilization of vaccines, biologics and other heat sensitive drugs. The process helps to maintain the structural integrity and biological activity of the product, making it ideal for long term storage (Rustemi-Ahmeti H et al., 2025)

Despite the substantial progress achieved in recent years, several important challenges remain unresolved, including optimization of tumor retention time, standardization of dosimetry protocols, radionuclide selection, long-term toxicity evaluation, and validation through large prospective clinical trials (Hicks RJ, 2025). Therefore, continued research is essential to fully establish the clinical role of FAPI-based radiopharmaceuticals in precision oncology.

Biological Background of Fibroblast Activation Protein

Fibroblast activation protein (FAP) is a type II transmembrane glycoprotein belonging to the dipeptidyl peptidase family. It exhibits both dipeptidyl peptidase and endopeptidase activity and plays a significant role in extracellular matrix remodeling, tissue repair, fibrosis, wound healing, and tumor progression. Under normal physiological conditions, FAP expression is generally absent or very limited in healthy adult tissues. However, FAP becomes highly expressed in activated fibroblasts associated with chronic inflammation, fibrosis, and malignant tumors (Watabe T et al., 2020).

Cancer-associated fibroblasts represent one of the dominant cellular components of the tumor microenvironment and contribute significantly to tumor development and progression. CAFs promote angiogenesis, immune suppression, tumor cell proliferation, invasion, and metastasis through the secretion of cytokines, growth factors, extracellular matrix proteins, and signaling molecules. Elevated FAP expression has been reported in multiple malignancies, including pancreatic adenocarcinoma, breast carcinoma, colorectal cancer, ovarian cancer, hepatocellular carcinoma, and sarcomas (Loktev A et al., 2019).

The selective overexpression of FAP in tumor-associated fibroblasts while remaining minimally expressed in healthy tissues makes FAP an ideal molecular target for theranostic applications. Targeting the tumor microenvironment rather than only malignant cells represents an important paradigm shift in oncology and may improve diagnostic sensitivity and therapeutic efficacy.

Development of FAPI-Based Radiopharmaceuticals

The development of FAPI-based radiopharmaceuticals represents a major advancement in targeted molecular imaging and radionuclide therapy. Early FAP inhibitors demonstrated insufficient affinity and suboptimal pharmacokinetic properties, limiting their clinical utility. However, the development of quinoline-based FAPI compounds significantly improved tumor targeting, biodistribution, and clinical applicability (Loktev A et al., 2019).

Several FAPI compounds have been developed over recent years, including FAPI-02, FAPI-04, FAPI-21, FAPI-46, and FAP-2286. Among these compounds, FAPI-04 and FAPI-46 demonstrated particularly favorable pharmacokinetic characteristics, including rapid tumor uptake and improved tumor retention time. Chelators such as DOTA and NOTA are commonly incorporated into FAPI molecules to facilitate stable radiolabeling with both diagnostic and therapeutic radionuclides (Czuczejko J et al., 2026).

Gallium-68 remains one of the most frequently used radionuclides for FAPI PET imaging because of its favorable decay properties and accessibility through generator systems. Fluorine-

18-labeled FAPI radiopharmaceuticals have also attracted increasing interest because of their longer half-life and suitability for centralized production and large-scale distribution. In therapeutic applications, radionuclides such as Lutetium-177 and Actinium-225 are increasingly utilized because of their cytotoxic beta- and alpha-particle emissions (Ballal S et al., 2021).
Optimization of molecular structure, linker design, and radionuclide selection remains essential for improving tumor retention and maximizing therapeutic efficacy. Current research focuses on developing next-generation FAPI radiopharmaceuticals with improved pharmacodynamics and prolonged intratumoral retention.

Diagnostic Imaging Applications

4.1 FAPI PET/CT Imaging: FAPI PET/CT imaging has emerged as one of the most promising diagnostic applications in modern oncologic imaging. Gallium-68-labeled FAPI radiopharmaceuticals have demonstrated remarkable diagnostic performance across a wide range of malignancies due to their high tumor uptake and low physiological accumulation in normal tissues (Giesel FL et al., 2019).
Compared with conventional 18F-FDG PET/CT imaging, FAPI PET imaging offers several important advantages. Physiological uptake in the brain, liver, oral cavity, and gastrointestinal tract is generally low, allowing improved lesion detection in these regions. In addition, FAPI imaging does not require prolonged fasting or blood glucose monitoring before image acquisition, thereby simplifying imaging protocols and improving patient convenience (Kratochwil C et al., 2019).
Fluorine-18-labeled FAPI radiopharmaceuticals are increasingly being investigated because they may provide improved spatial resolution and logistical advantages associated with centralized cyclotron production. Clinical studies suggest that FAPI PET imaging may improve diagnostic sensitivity, especially in tumors characterized by extensive stromal desmoplasia.

4.2 Clinical Applications in Oncology
Pancreatic Cancer
Pancreatic ductal adenocarcinoma exhibits intense stromal fibrosis and abundant FAP expression, making it an excellent target for FAPI imaging. FAPI PET/CT has demonstrated superior tumor delineation and improved lesion contrast in pancreatic malignancies.
Breast Cancer
FAPI imaging has shown promising diagnostic performance in primary and metastatic breast cancer, especially in invasive lobular carcinoma and metastatic lesions with low FDG avidity.
Lung Cancer
In non-small cell lung cancer, FAPI PET imaging has demonstrated favorable lesion visualization and may improve detection of metastatic disease.
Colorectal Cancer
FAPI PET imaging has demonstrated high sensitivity in detecting recurrent and metastatic colorectal cancer, particularly peritoneal metastases.
Additional Malignancies
Promising results have also been reported in ovarian cancer, gastric cancer, cholangiocarcinoma, hepatocellular carcinoma, sarcomas, and head and neck tumors.

FAPI-Based Targeted Radionuclide Therapy

The integration of diagnostic imaging and targeted radionuclide therapy within a single molecular platform represents the core principle of theranostics. In FAPI theranostics, diagnostic radionuclides are used for tumor visualization and patient selection, while therapeutic radionuclides deliver cytotoxic radiation directly to the tumor microenvironment.
Lutetium-177-labeled FAPI radiopharmaceuticals are currently among the most extensively investigated therapeutic compounds because of their favorable beta-particle emission and simultaneous imaging capability. FAPI compounds labeled with alpha-emitting radionuclides such as Actinium-225 offer highly potent localized cytotoxicity with minimal surrounding tissue damage (Wu X et al., 2025).
FAPI radionuclide therapy primarily targets cancer-associated fibroblasts and stromal components, disrupting the supportive tumor microenvironment essential for malignant progression. Preliminary clinical studies have demonstrated encouraging therapeutic responses, pain palliation, and symptom improvement in patients with advanced and treatment-resistant malignancies (Ballal S et al., 2021).
Although initial results are promising, most currently available data originate from small early-phase clinical studies. Large multicenter prospective trials remain necessary to establish standardized treatment protocols and evaluate long-term therapeutic efficacy and safety.

Safety, Toxicity, and Dosimetry

Radiation dosimetry represents an essential component of targeted radionuclide therapy because it directly influences treatment efficacy and toxicity. Current evidence suggests that FAPI-based radiopharmaceuticals generally demonstrate favorable safety profiles with relatively limited severe adverse effects (Hicks RJ, 2025).
The kidneys, bone marrow, liver, and salivary glands represent potential organs at risk depending on the selected radionuclide and radiopharmaceutical characteristics. Reported adverse effects include mild hematologic toxicity, fatigue, nausea, and transient discomfort, although severe toxicity appears relatively uncommon in currently available studies.
One of the primary limitations of therapeutic FAPI radiopharmaceuticals remains relatively short tumor retention time, which may reduce the delivered radiation dose to tumors and limit therapeutic effectiveness. Consequently, significant research efforts are directed toward improving molecular design, increasing tumor retention, and optimizing dosimetry strategies.
Long-term toxicity data remain limited because most FAPI therapeutic applications are still in early clinical development. Future prospective studies will be essential for determining long-term safety and establishing standardized dosimetry protocols.

Challenges and Limitations

Despite their considerable promise, FAPI-based radiopharmaceuticals face several important challenges and limitations. One of the major concerns involves heterogeneous FAP expression between different tumor types and even within individual tumors. Furthermore, increased FAP expression may also occur in inflammatory and fibrotic diseases, potentially reducing imaging specificity.
Another major limitation relates to rapid radiopharmaceutical washout and insufficient tumor retention observed with some FAPI compounds. Optimization of linker systems, chelator design, and radionuclide selection remains critical for improving therapeutic efficacy.

Standardization of imaging protocols, dosimetry methods, and therapeutic regimens remains incomplete. In addition, most available clinical data are derived from small retrospective or early-phase studies, emphasizing the need for larger prospective multicenter investigations.
Economic considerations, production logistics, regulatory approval, and radiopharmaceuticals availability may also influence the widespread clinical implementation of FAPI theranostics.

Future Perspectives

The future of FAPI-based theranostics appears highly promising. Development of next-generation FAPI radiopharmaceuticals with prolonged tumor retention and improved pharmacokinetic characteristics remains a major research focus. Novel compounds incorporating albumin-binding motifs and alternative linker systems may significantly enhance therapeutic efficacy.
Combination therapies involving immunotherapy, chemotherapy, targeted therapy, and external beam radiotherapy may further improve clinical outcomes. Artificial intelligence and quantitative imaging techniques may also contribute to improved lesion characterization, treatment planning, and therapy monitoring.
Beyond oncology, FAPI imaging may also have potential applications in fibrotic and inflammatory diseases, including cardiac fibrosis, pulmonary fibrosis, liver cirrhosis, rheumatoid arthritis, and inflammatory bowel disease.
As precision medicine continues to evolve, FAPI-based radiopharmaceuticals are expected to become increasingly important tools in individualized cancer diagnosis and therapy.

Conclusion

FAPI-based radiopharmaceuticals represent one of the most significant recent advancements in nuclear medicine and precision oncology. Their ability to target cancer-associated fibroblasts within the tumor microenvironment provides unique opportunities for both diagnostic imaging and targeted radionuclide therapy. FAPI PET/CT imaging has demonstrated excellent diagnostic performance across multiple malignancies, while therapeutic FAPI compounds have shown encouraging preliminary clinical outcomes in advanced cancers.
Although several important challenges remain unresolved, including tumor retention optimization, dosimetry standardization, and long-term safety evaluation, ongoing scientific research continues to expand the clinical potential of FAPI theranostics. Future developments in molecular design, radionuclide selection, and combination treatment strategies are expected to further strengthen the role of FAPI-based radiopharmaceuticals in personalized oncology and precision medicine.

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