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Fibroblast Activation Protein Inhibitors: Structural Evolution, Binding Mechanisms, and Theranostic Applications in Positron Emission Tomography/Computed Tomography Imaging

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Abstract. α-Fibroblast activation protein (α-FAP) is overexpressed in cancer-associated fibroblasts within the tumor microenvironment of most epithelial cancers, making it an attractive target for cancer-specific imaging and therapy. This article summarizes the structural features, binding mechanisms, radiolabelling strategies, and clinical potential of FAP inhibitors (FAPIs). FAPI molecules generally consist of three functional modules: a quinoline-based core for target recognition, a linker, and a DOTA/NOTA chelator for radionuclide labelling. The interaction between FAPIs and α-FAP is primarily mediated by several amino acid residues, each engaging a specific structural module of the inhibitor, but residues involved are not fixed and may shift with structural variation among FAPI derivatives. The evolution from early boronic acid compounds to UAMC-1110 marks a transition from non-selective dipeptidyl peptidase inhibitors toward FAP-selective warheads, while later modifications (e.g., cyano to α-ketoamide) addressed the need for prolonged target residence. PET/CT is the combination of functional and structural scanning, increasing diagnostic accuracy. The same targeting principle also enables therapeutic applications when labelled with β-emitting radionuclides. The clear specificity of FAPI also helps overcome many limitations of ^{18}F-FDG.

Keywords: FAPI, Cancer-associated fibroblasts, PET-CT, Radiopharmaceuticals, Structure-activity relationship (SAR)

1. Introduction

Cancer remains one of the leading causes of death worldwide, and early diagnosis is critical for improving patient outcomes. Medical imaging plays an essential role in cancer detection, staging, treatment and monitoring. Among various imaging modalities, positron emission tomography (PET) /computed tomography (CT) has become a cornerstone of modern oncology because it provides both functional and anatomical information in a single scan.

The most widely used PET tracer is ^{18}F-fluorodeoxyglucose ([^{18}F]FDG) that measures glucose metabolism. Most malignant cells exhibit enhanced glycolytic activity while well-differentiated

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tumors and mucinous carcinomas may show low tracer uptake, and the relative avidity depends on glucose transporter and hexokinase expression levels [1]. However, ^{18}F-FDG has several limitations [1]. In recent years, fibroblast activation protein (FAP) has emerged as a promising new target for cancer imaging. FAP is a protease highly expressed on cancer-associated fibroblasts (CAFs) within tumor microenvironment of most cancers, while showing limited expression in normal adult tissues [2]. This makes FAP an ideal target for tumor-specific imaging. Small-molecule FAP inhibitors (FAPIs) labeled with positron-emitting radionuclides such as ^{68}Ga and ^{18}F have been developed and have shown excellent imaging performance in studies.

This review provides an overview of FAPI-based PET imaging, including the biology of FAP, the structural features of FAPIs, binding mechanisms, the evolution of FAPI, radiolabeling strategies, PET/CT imaging principles, and the advantages of FAPI over [^{18}F]FDG.

2. Biological basis and structural characteristics of FAP

Fibroblasts are widely accepted to be spindle-shaped cells that express vimentins. They are generally embedded within fibrillar ECM as single resting mesenchymal cells in normal tissues [3]. Cancer cells actively recruit fibroblasts through the secretion of chemokines and growth factors such as fibroblast growth factor and transforming growth factor-β. Once recruited, fibroblasts get activated to CAFs and begin to recruit additional fibroblasts and participate in tumor-promoting functions [2]. Their roles in immune evasion, chemoresistance, and tissue remodelling drive tumor invasiveness and metastasis [2]. As cancers evolve, CAFs evolve into different phenotypes [3]. The processes are highly related to FAPs that are overexpressed on the membrane of CAFs in over 90% epithelial cancers [2, 4].This makes both CAFs and FAP sufficiently cancer-specific to serve as cancer targets.

As illustrated in Fig.1, α-FAP is a homodimer with two identical subunits, each composed of 760 amino acids. The glycosylated protein is surrounded by sugar moieties (blue cubes) and water molecules (red dots). FAP, a type II membrane-bound serine protease, belongs to dipeptidyl peptidase 4 (DPP-4) family. It cleaves peptide hormones and further degrades denatured collagen after cleavage by matrix metalloproteinases. In addition to enzymatic functions, FAP also contributes to tumor growth [2]. The structure of FAP provides multiple amino acid residues that can be targeted by inhibitors. Typical FAPIs engage the protein through non-covalent bonds, while newer generations are designed to form covalent bonds with FAP to enhance binding duration.

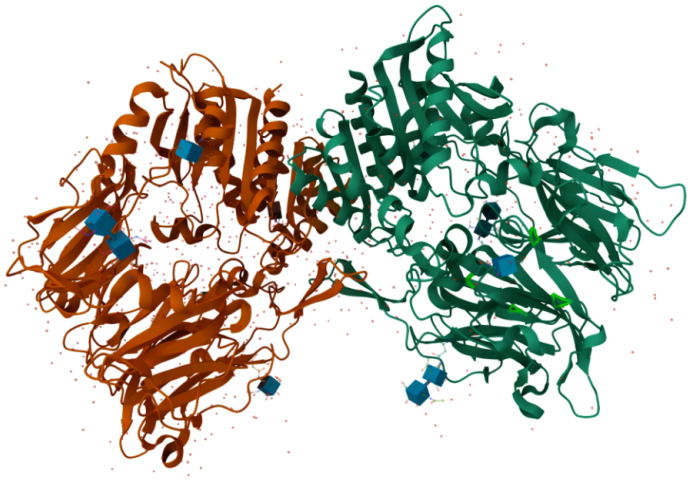


Figure 1. Crystal structure of α-FAP (PDB: 1Z68)

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3. Structural design and classification of FAPIs

3.1. The basic structure of modern FAPIs

As shown in Fig.2, a typical FAPI molecule consists of three functional moieties: a quinoline-cyanopyrrolidine conjugation, a linker, and a chelator [5]. The cyanopyrrolidine is primarily responsible for target recognition and conjugation with FAP, while the quinoline ring enhances overall selectivity and facilitates linkage to the rest of the molecule. The quinoline-cyanopyrrolidine conjugation serves as the core recognition unit. Piperazine-based linkers are particularly common, and variety increases as structural optimization goes further [5]. The chelator, whose nitrogen lone pairs coordinate with radionuclides, enables machine visualization. While DOTA and NOTA are compatible with most clinically used radionuclides, alternative chelators has been developed to accommodate a broader spectrum of ions (Fig.3) [5]. FAPIs can be engineered either for diagnostic detection of FAPs in tissues or therapeutic inhibition of FAP activity.

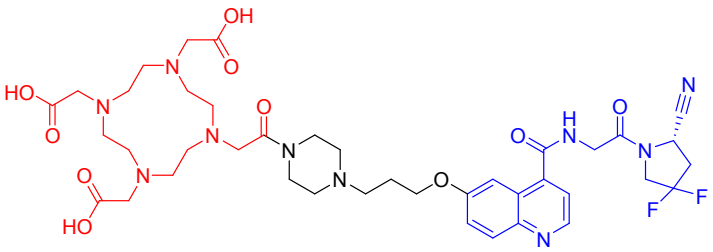


Figure 2. Chemical structure of FAPI-04 highlighting three functional modules: cyanopyrrolidine core (blue), piperazine linker (black), and DOTA chelator (red)

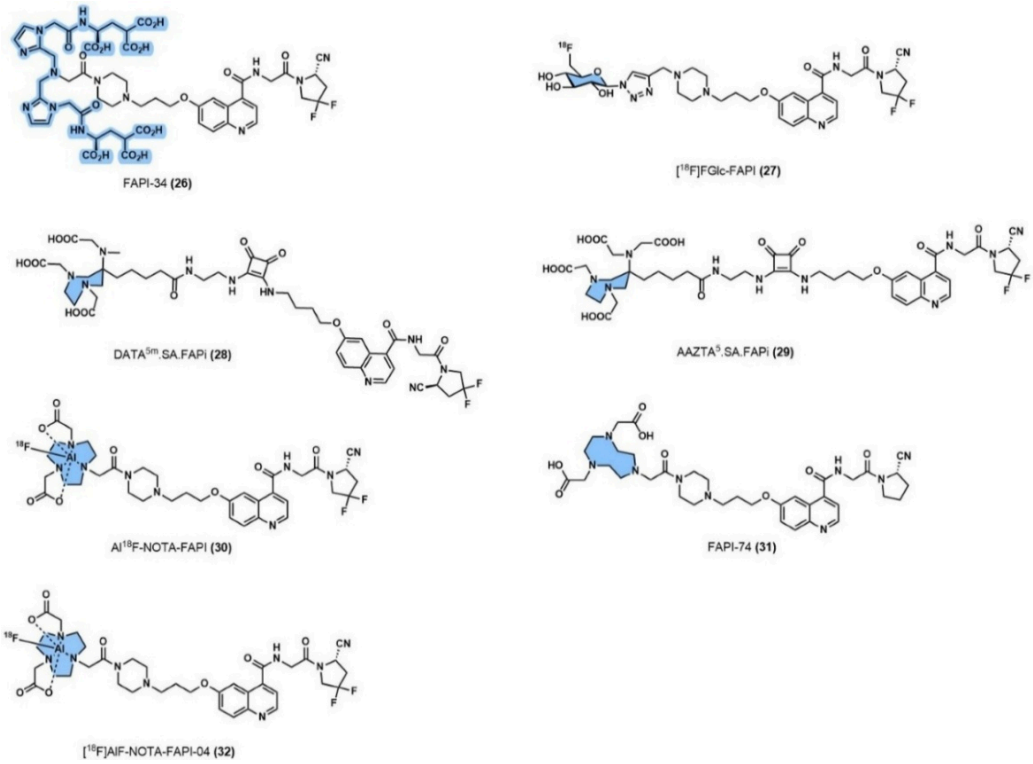


Figure 3. Different chelators used in various FAPIs (blue) [5]

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3.2. Generations of FAPIs

3.2.1. From antibodies to molecules: the development of the core cyanopyrrolidine part

In early development of FAPI, antibodies were first introduced. The ^{131}I-labeled murine monoclonal antibody mAb F19 was initially reported to detect lesions as small as 1 cm in diameter at 3-5 days after injection in murine models [2]. However, the humanized version demonstrated limited efficiency in most patients, and the time required for imaging is too long. Moreover, the optimal radionuclides for antibody labelling possessed excessively long half-lives, introducing additional challenges to manage radioactive wastes [2]. These limitations suggested that smaller inhibitors were necessary. Then people shifted toward peptide-based agents. Although peptides exhibited faster circulation and clearance [5], they remained relatively large and required complex cyclization synthesis steps. Ultimately, these investigations led to the discovery of small molecules.

A breakthrough came with Val-boroPro, or PT-100 (Fig.4, compound 1). The boronic acid-based compound demonstrated FAP inhibitory activity through interaction with bone marrow stromal cells [5]. However, PT-100 also inhibited DPP-IV, DPP8, and DPP9 due to its inherent dipeptidyl peptidase activity. To address these selectivity issues, researchers synthesized a series of N-acyl-Gly-, N-acyl-Sar-, and N-blocked-boroPro derivatives and systematically investigated their structure-activity relationships [5]. To further improve selectivity, the boronic acid moiety was replaced with a carbonitrile group. Fluorine substituents were introduced to enhance inhibitory activity, and a quinoline group was incorporated to optimize binding affinity to FAP. Collectively, these efforts led to the identification of UAMC-1110 (Fig.4, compound 14), the most promising FAP-targeting molecule at the time [4, 5]. The compounds shown in Fig.4 represent key intermediates during the development of early generations.

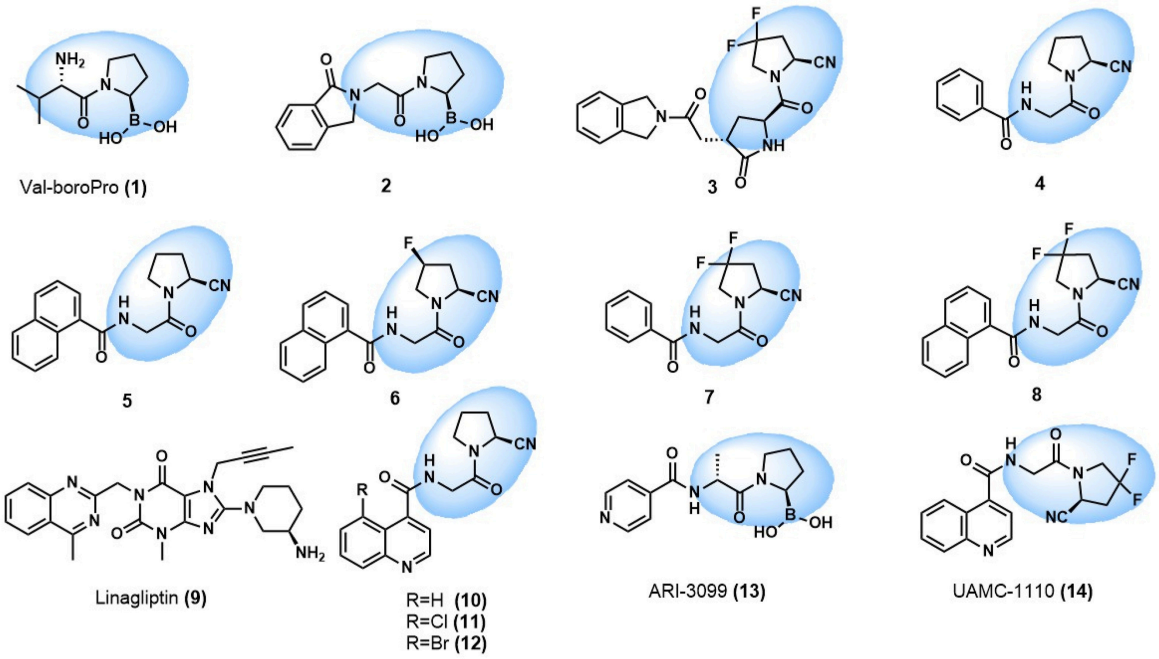


Figure 4. Chemical structures of the FAP inhibitor lead PT-100 (1), synthetic intermediates (2–13), and the optimized candidate UAMC-1110 (14) [5]

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3.2.2. The formation of modern 3-moiety structure

Based on UAMC-1110, subsequent FAPI development focused on modifying the quinoline side chain to enable conjugation with DOTA, NOTA, or other chelators for radionuclide labeling. Early efforts involved attaching iodine directly to the quinoline moiety for diagnostic applications (Fig.5, compound 15) [5]. However, this approach was compromised by deiodination which causes biological activity loss. To circumvent this limitation, researchers pursued alternative strategies by incorporating chelators onto the quinoline side chain, resulting in the non-halogenated derivative FAPI-02 (Fig.5, compound 16). This design not only provided greater flexibility in coordinating with metal ions but also rendered the compound applicable to both diagnostic and therapeutic settings [5]. In addition, the linker moiety contributed to overall molecular stability. Subsequently, a series of optimized derivatives, including FAPI-04, FAPI-21, and FAPI-46, were developed to further reduce false-positive rates, enhance selectivity, and improve biological activity [5]. Concurrently, a broader range of radionuclides was evaluated to achieve optimal performance across different clinical applications.

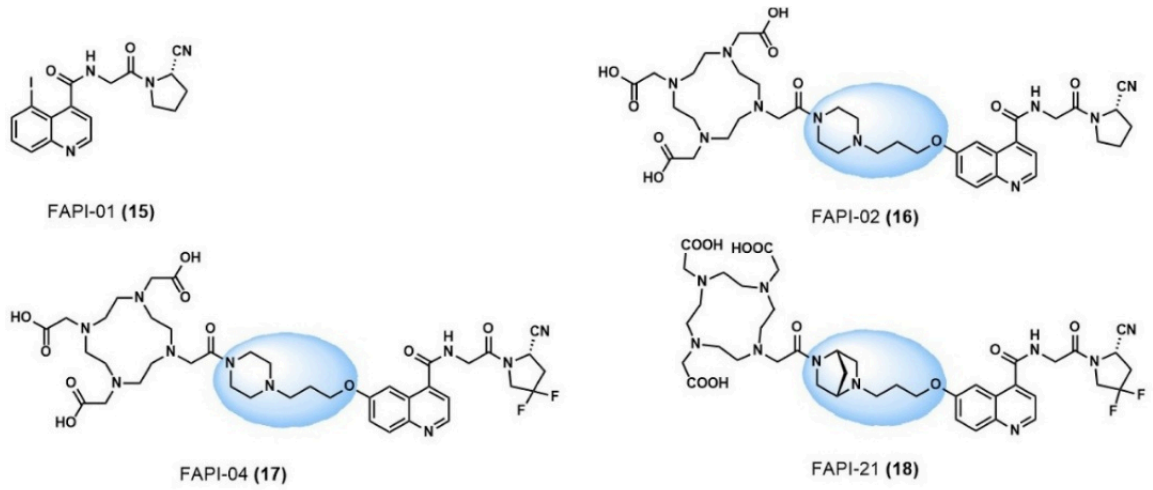


Figure 5. Chemical structures of FAPI-01 (15), FAPI-02 (16), FAPI-04 (17), and FAPI-21 (18) featuring simple linkers and chelators [5]

The modification of linkers represents a noteworthy direction in FAPI optimization. DOTA.SA.FAPi (Fig.6, compound 20) was the first molecule to introduce a squaramide linker [5]. Studies indicated that this compound maintained both FAP binding affinity and satisfactory stability, while demonstrating efficiency and favorable safety in preclinical evaluations. OncoFAP-DOTAGA (Fig.6, compound 21), which features an amide-based linker, exhibited higher tumor uptake compared to FAPI-46. The success of OncoFAP-DOTAGA subsequently stimulated interest in linear linkers, leading to the discovery that polyethylene glycol (PEG) moieties could prolong in vivo half-life of FAPIs, whose examples are compounds 23 and 24 in Fig.6 [5].

Additionally, [^{18}F]AlF-P-FAPI (Fig.6, compound 24) introduced a novel radiolabeling approach in which aluminum coordinates with NOTA and ^{18}F through four coordinate bonds. This method has also proven to be sufficiently effective for practical applications [5].

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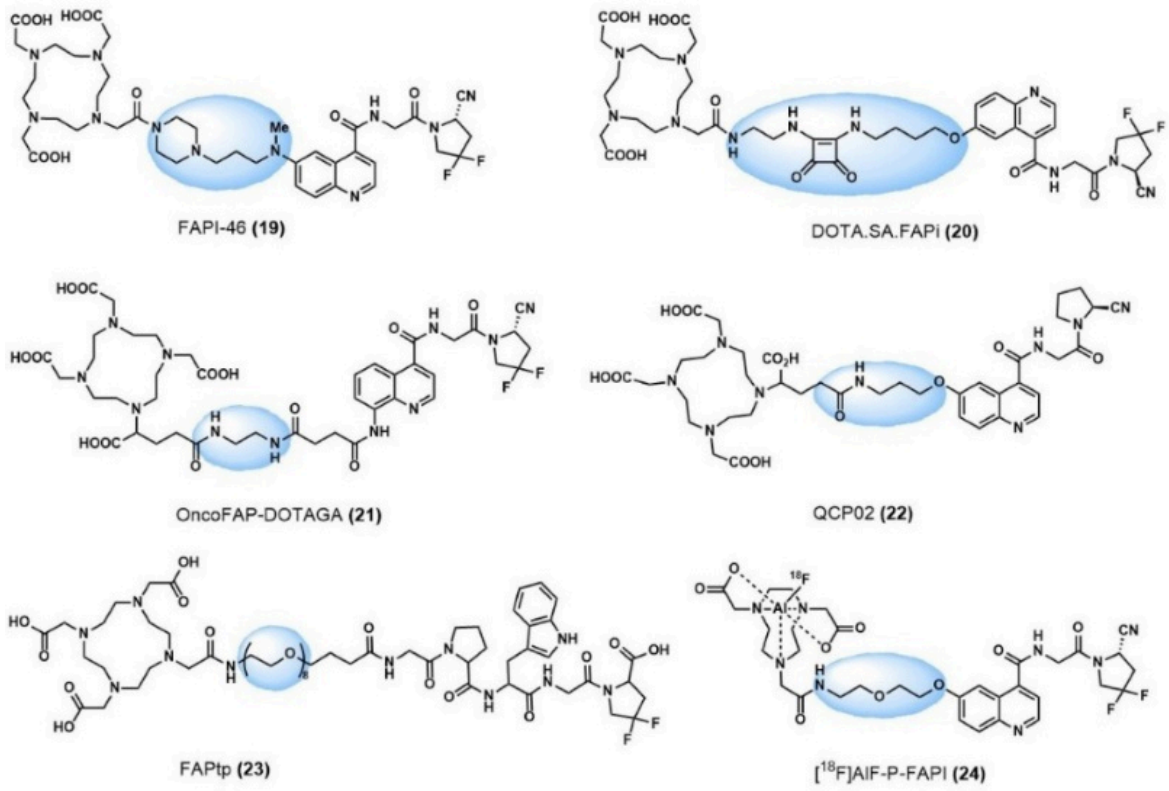


Figure 6. Squaramide linker (20), amide linker (21), and PEG linker (23, 24) [5]

3.3. The application of multimers

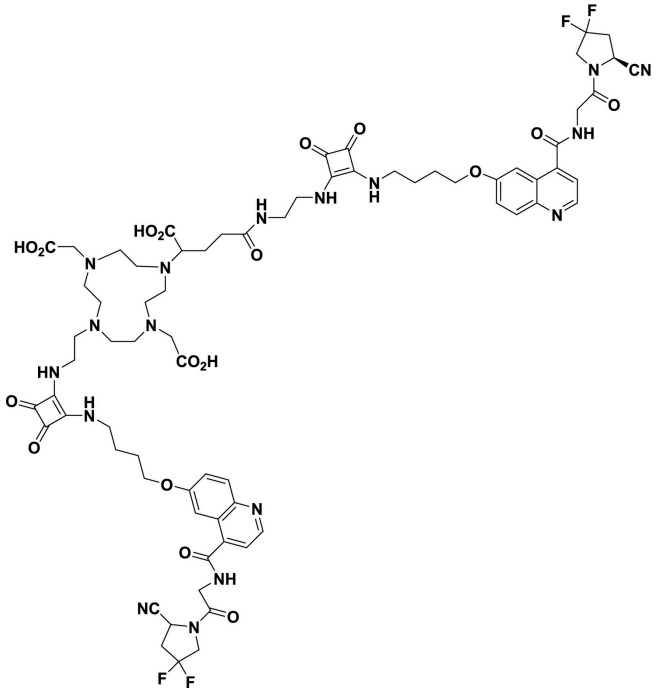


Figure 7. Chemical structure of [177Lu]Lu-DOTA.SA.FAPi [6]

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In addition to structural modification of monomeric FAPIs, an alternative strategy to improve pharmacokinetic performance is multimerization, meaning to link two or more FAPI units into a single multimeric molecule. This approach prolongs in vivo half-life of FAPI and increases residence time within tumor microenvironment. A variety of radionuclides have been evaluated for compatibility with multimerized FAPIs. A representative structure of a multimerized FAPI is shown in Fig.7 [6], in which the squaramide linker connects the DOTA chelator to the FAP-recognition units.

3.4. The addition of evans blue (EB)

Another alternative to prolong half-life and improve pharmacokinetics and pharmacodynamics is adding additional functional groups such as EB. Fig.8 shows general structure of EB-modified FAPIs, in which EB binds with the hydrophilic linker. EB exhibits high affinity with albumin. As this combination is reversible, the drug-albumin complex optimizes drug distribution and bioavailability. Experiment shows that while maintaining high affinity with albumin and FAP targeting specificity, EB-modified FAPIs outperform normal ones in tumor uptake and tumor growth suppression [7].

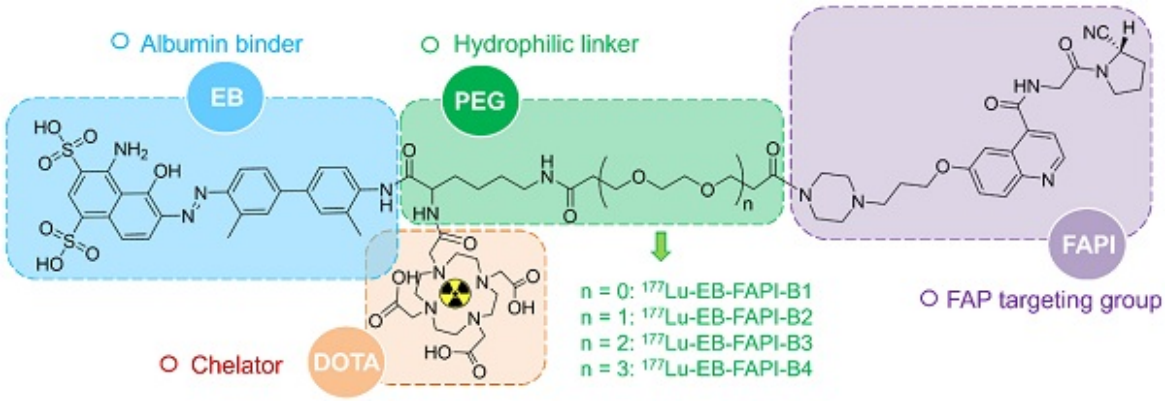


Figure 8. General structure of EB-modified FAPIs with combination of FAPIs and EB [7]

3.5. Binding method between the protein and the inhibitor

For diagnostic applications, non-covalent interactions represent the predominant mode of binding between FAPI inhibitors and the FAP target. Due to large variety of FAPI family and complex structure of FAP, small structure change, such as the addition of nuclides in FAPI, means alternative amino acid residues involved in binding. Meanwhile, GOLD software is used to calculate the most possible docking pose of the inhibitor-protein complex. In Fig.9, ^{177}Lu-FAPI-04 binds with residues of S624, H734, Y541, E204 and W295 [8], while in Fig.10, FAPI-04 binds with D60, W155, K209, and W298, explained by an electrostatic potential graph [5]. This suggests that various structures may be applied in reality, and a general binding "rule" remains mysterious.

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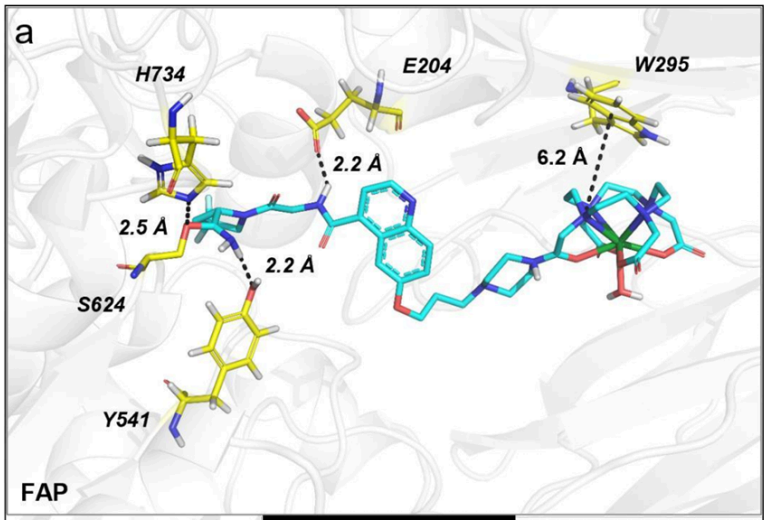


Figure 9. A possible docking pose of 177Lu-FAPI-04 and FAP calculated by GOLD [8]

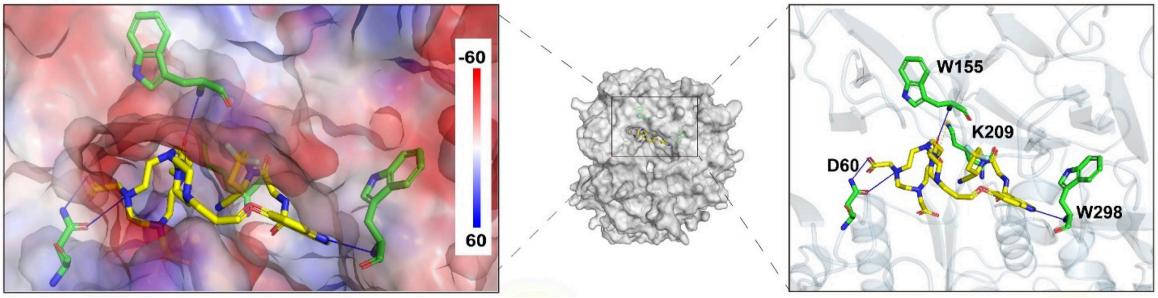


Figure 10. Electrostatic potential of FAP and FAPI-04 (left), and possible docking pose (right) [5]

In the context of therapeutic applications, covalent bonding offers the advantage of enhanced stability, thereby prolonging the in vivo half-life of the inhibitor and improving tumor retention. The carbonitrile group, commonly referred to as the "warhead", has been shown to form a reversible covalent bond with residues Ser624 and His734 [9]. However, the electrophilicity of the carbonitrile moiety is insufficient to maintain this bond over extended periods. To address this limitation, researchers have replaced the carbonitrile with an α-ketoamide group, giving rise to a new class of compounds termed "ketoFAPI" shown in Fig.11 [9]. This modification has been demonstrated to significantly extend target residence time, a critical parameter for effective radionuclide therapy.

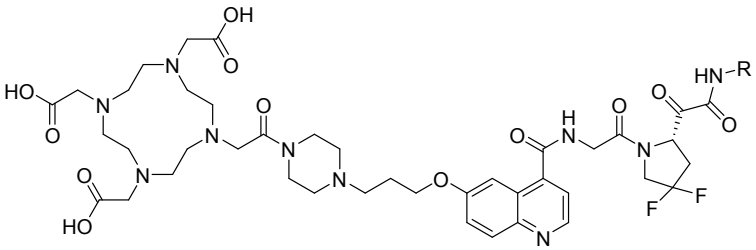


Figure 11. General structure of "ketoFAPI" [9]

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4. Comparison and advantages over [^{18}F]FDG

Glucose analogue 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) has been the most widely used radiopharmaceutical for PET/CT in oncology for decades. As [^{18}F]FDG is a modified glucose molecule, cells absorb [^{18}F]FDG as glucose, so uptake of [^{18}F]FDG in cells reflects glycolytic activity. Tumor cells consume glucose at rates significantly higher than normal cells because of the upregulation of glucose transporters and hexokinase enzymes, increased neo-angiogenesis, the number of viable tumor cells, and their aggressiveness and proliferative activity. This result in higher metabolism of [^{18}F]FDG. Therefore, [^{18}F]FDG can detect many cancers with the help of radionuclide detectors.

However, [^{18}F]FDG uptake faces several limitations. High physiological background activity in organs such as the brain, liver, and intestines can obscure adjacent lesions and reduce image contrast. Glucose transporter and hexokinase expression vary significantly across tumor types and grades. Well-differentiated tumors, mucinous carcinomas, and certain hepatocellular carcinomas often show low or absent [^{18}F]FDG uptake [1]. Most critically, [^{18}F]FDG lacks specificity for cancer. Acute inflammation, infection, wound healing, and benign tumors also increase glucose metabolism and result in false positive findings. This is particularly problematic in patients with concurrent inflammatory conditions, which are common in cancer populations.

By contrast, FAPIs target FAPs, specifically overexpressed on cancer-associated fibroblasts in the tumor stroma of over 90% epithelial cancers and underexpressed in normal adult tissues [2]. This antigen-antibody recognition confers FAPI with significantly higher specificity for malignant cancers, lowers false-positive rates and improves diagnostic accuracy. For most cancer types, FAPI PET/CT has demonstrated superior lesion detection and higher tumor-to-background ratios compared to [^{18}F]FDG. To be complete, [^{18}F]FDG retains certain advantages in some cancers, such as lymphomas and some hematological tumors, where FAP expression is less prominent or rapid glucose metabolism remains the most reliable functional marker [1]. In these cases, using both tracers may offer optimal diagnostic accuracy, but doubling radionuclide intake is not preferred for patients' safety. Further development of next-generation FAPIs with broader applicability remains an active area of research.

5. The principle and optimization of imaging technology

The development of FAPIs has been driven by imaging technology, particularly PET. PET is designed to detect positron-emitting radio nuclides, the most used isotopes for diagnostic imaging [10]. After radionuclides decay, positrons are released. The positrons travel a short distance in tissue before encountering electrons. One positron and one electron annihilate and convert into two 511-keV γ-photons that travel in opposite directions with the same speed. The PET scanner consists of a ring of detectors to identify these γ-photon pairs. By collecting millions of such events, the scanner determines the line along which the annihilation occurred. Then this information is converted into a 3D image of radionuclide distribution by algorithms [10], suggesting the location of radioactive FAPIs.

However, as γ-photons travel through the body, some are absorbed or scattered by tissues as energy. Attenuation reduces signal intensity and introduces errors, so attenuation correction is required [11]. CT can be used here. CT images with anatomical information is converted into an attenuation map that corrects PET data for signal loss. The integration of PET and CT not only enables accurate attenuation correction but also provides precise anatomical localization of functional signals, increasing diagnostic accuracy from 91% to 98%. As Fig.12 shows, A typical

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PET/CT examination begins with a low-dose CT scout scan for positioning, followed by the diagnostic CT and PET acquisitions, and concludes with image fusion [11].

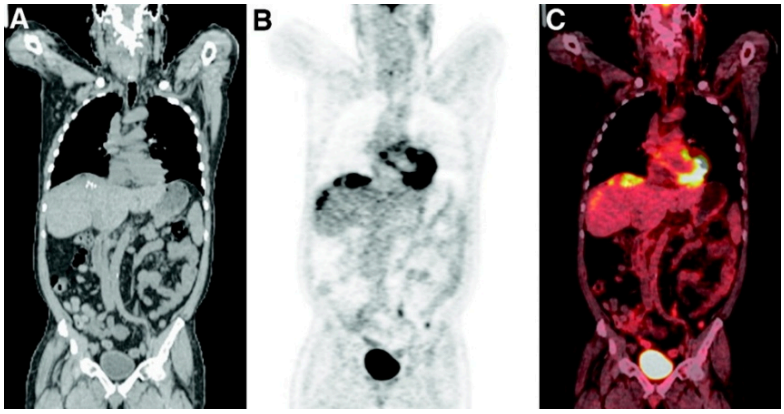
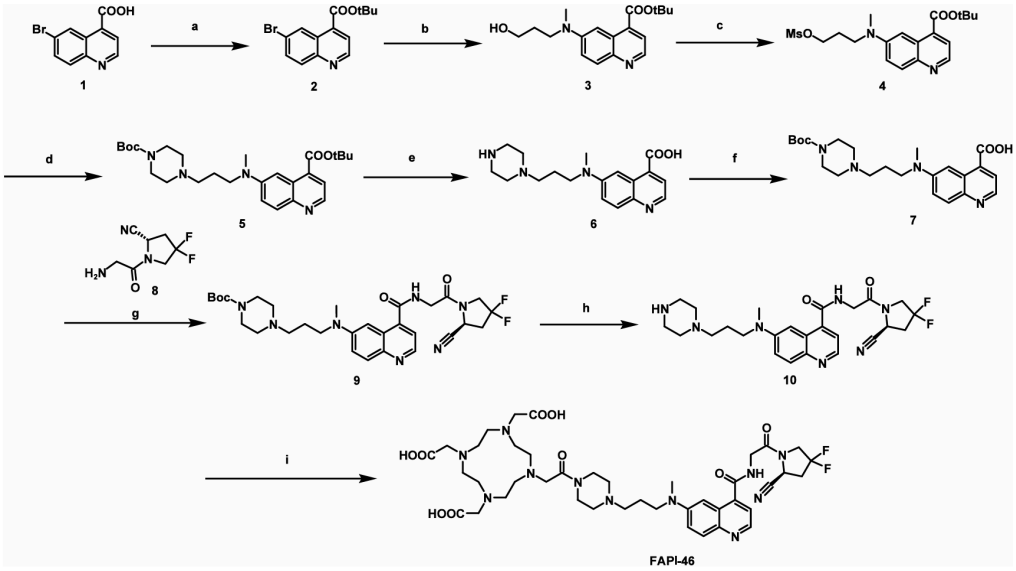


Figure 12. Coronal whole-body CT image (A), PET image with CT attenuation correction (B), and fused image (C) [11]

6. Brief organic and inorganic synthesis



"Reagent and conditions: (a) O-tert-butyl-*N*,*N*′-dicyclohexylisourea, Et_3N, THF, 50 °C, over night, 44%; (b) $HO(CH_2)_3NHMe$, $Pd_2(dba)_3$, BINAP, Cs_2CO_3, toluene, 90 °C, overnight, 62%; (c) CH_3SO_2Cl, Et_3N, CH_2Cl_2, rt, 1 h; (d) 1-Boc-piperazine, KI, Et_3N, DMF, 70 °C, 2.5 h, 84%; (e) TFA, triisopropylsilanol, TfOH, CH_2Cl_2, 0 °C-rt, 1 h; (f) di-tert-butyl decarbonate, Et_3N, DMF, 0 °C-rt, 1 h, 65%; (g) HBTU, HOBt, DIPEA, DMF, rt, over night, 37%; (h) TFA, MeCN, rt, 15 min; (i) DOTA-p-nitrophenol ester, Et_3N, DMF, rt, 2 h, 85%. Adapted with permission from [J. Nucl. Med., 2019, 60, 1421.]. Copyright [2019] [the Society of Nuclear Medicine and Molecular Imaging].

Figure 13. One synthesis route of FAPI-46 [12]

The synthesis of FAPI radiopharmaceuticals comprises two distinct components: organic synthesis of the targeting scaffold and inorganic radiolabeling of the chelator-metal complex. For the organic component, FAPI-46 as a representative example, most synthetic routes follow a modular assembly approach. The quinoline core is typically constructed first, followed by the introduction of the linker, the subsequent attachment of the bioactive cyanopyrrolidine, and finally the conjugation of the chelator. Although multiple synthetic strategies exist for each moiety, the overall sequence of assembly remains largely consistent across different routes. Fig.13 shows one of the synthesis routes of FAPI-46 [12], where the quinoline core is constructed via a Pfitzinger or Friedländer

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condensation, followed by amide coupling with piperazine-based linkers using EDCI/HOBt activation. The stereoselective construction of the 2-cyanopyrrolidine warhead remains a critical challenge because the C2 proton is mildly acidic and susceptible to epimerization under basic conditions. Phase-transfer alkylation of the glycine-derived Schiff base and chiral pool strategies starting from L-proline both provide access to the desired enantiomer with >20:1 dr; current routes using EDCI/HOBt-mediated amide coupling proceed with minimal racemization when conducted below 0 °C [12]. Recent advances have focused on streamlining this step through asymmetric catalysis or chiral pool synthesis, improving overall yields from <15% to >40%. The final DOTA conjugation is performed under mild aqueous conditions to avoid hydrolysis of the sensitive nitrile moiety.

The radiolabeling step involves inorganic coordination chemistry. Under controlled pH and temperature conditions, the metal ion forms coordinate bonds with the nitrogen donor atoms of the chelator. This process is essentially an acid-base neutralization reaction, where the chelator acts as a Lewis base that donates electron pairs to the metal cation, which serves as a Lewis acid. Inorganic salts and buffer solutions are commonly used to maintain the optimal reaction conditions. Fig.14 shows some methods to make coordinate bonds on FT-FAPIs [13].

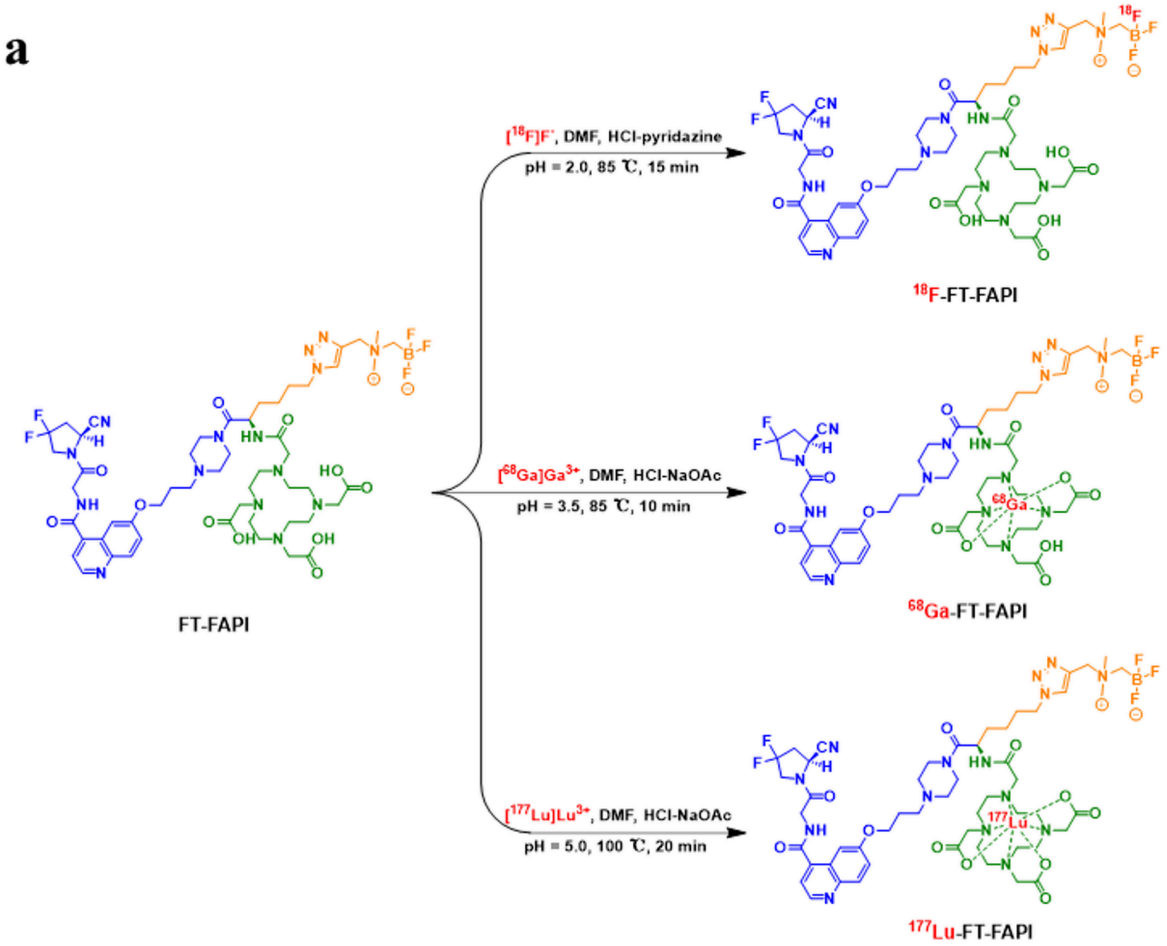


Figure 14. Typical inorganic conditions to produce radioactive FAPIs and respective products

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7. *In vivo* metabolism of FAPIs

The pharmacokinetic profile of FAPI tracers is characterized by rapid tumor accumulation (Fig.15b), fast blood clearance (Fig.15d), predominant renal excretion (Fig.15a), and low healthy organ uptake (Fig.15a, c). For the specific variant FT-FAPI, quantitative biodistribution studies in mice revealed moderate bone uptake, a finding that warrants consideration for bone-metastasis imaging but does not compromise the overall favorable safety profile observed in early human studies [13].

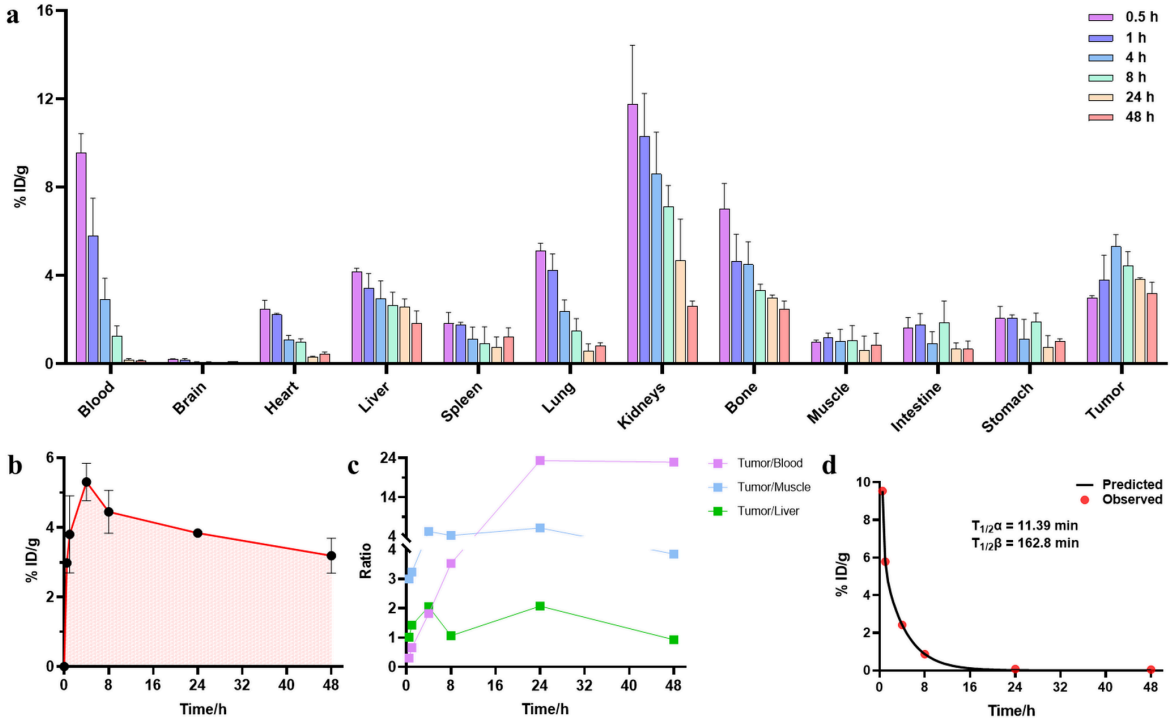


Figure 15. Biodistribution (a), time curve of tumor uptake (b), time curves of the uptake ratio for tumor with organs (c), time-blood concentration profile (d) of 177Lu-FT-FAPI in mice [13]

8. Conclusion

This review has examined FAPI-based radiopharmaceuticals as a class of targeted imaging and therapeutic agents for cancer and has focused on their structural features, binding mechanisms, development history, and diagnostic advantages over [^{18}F]FDG. The central finding is that FAPI tracers achieve high tumor specificity by targeting FAP, which is overexpressed in the stroma of most epithelial cancers while being nearly absent in normal tissues. This mechanistic distinction from metabolism-based [^{18}F]FDG imaging translates into lower background uptake, improved tumor-to-background contrast, and fewer false-positive findings in clinical practice.

FAPIs have evolved from early boronic acid-based compounds to UAMC-1110 and subsequently to modern FAPI-04 and FAPI-46. Recent optimizations, including multimerization, EB addition and warhead modification, significantly extend tumor residence time and enable therapeutic applications.

Looking forward, the primary challenge remains improving tumor retention for radionuclide therapy while minimizing off-target uptake. Future research should prioritize three directions: (i) warheads with fine-tuned electrophilicity to balance target-residence time against off-target reactivity; (ii) FAPI variants compatible with a wider spectrum of diagnostic and therapeutic

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radionuclides through chelator diversification; and (iii) prospective trials in tumor types where FAP expression is heterogeneous, to establish the complementary roles of FAPI and [^{18}F]FDG imaging. Additionally, the complementary use of FAPI and [^{18}F]FDG warrants further investigation in tumor types where FAP expression is variable.

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