Are FAP Theranostics Really Happening? Will Radiochemistry or Biology Win?

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Researchers from the University of Heidelberg, who have been pioneers in the field of fibroblast activation protein inhibitor (FAPI) tracer development, have provided a perspective on whether such theranostics are happening (1). Their discussion reflects a deep understanding of radiopharmaceutical advances and briefly summarizes the immense amount of work done over the past 5 y leading to preliminary therapeutic trials. I have been asked to further comment on the challenges that face clinical translation of the promise of FAP-targeting theranostics from the perspective of my long involvement in therapeutic nuclear medicine, including being a very early adopter of peptide receptor radionuclide therapy (PRRT) and prostate-specific membrane antigen (PSMA) radioligand therapy, now collectively known as radiopharmaceutical therapy (RPT).

The principle "If you can see it, you can treat it," which underpins theranostics in general, is psychologically augmented by the corollary "If you can see little else, you can treat with low toxicity." Since the initial reports of radiopharmaceuticals targeting fibroblast activation protein (FAP) for diagnostic purposes, there has been great excitement regarding potential therapeutic application of related compounds. This enthusiasm has been stimulated by the high tumor-to-background activity ratios and preliminary indications that FAPI agents might outperform the diagnostic performance of the established oncologic standard, [¹⁸F]FDG. I have previously stated my own enthusiasm for FAP as a pan-cancer target (2). Thus, it was no surprise that one of the earliest reports of diagnostic FAPI agents also detailed a patient with metastatic breast cancer who was treated with 2.9 GBq of [90Y]Y-FAPI-04 under compassionate-use criteria (3). Posttreatment Bremsstrahlung imaging demonstrated significant tumor retention, and the patient experienced a symptomatic improvement in bone pain, encouraging further evaluation of the theranostic potential of these agents. However, despite a plethora of publications detailing the diagnostic efficacy of various radiolabeled FAP-targeting agents that have shown excellent diagnostic performance across a wide range of malignancies (4), there remain relatively few reports of successful therapeutic use of FAP radiopharmaceuticals. This contrasts somewhat with the early and successful translation of somatostatin analogs and PSMA ligands from diagnostic to therapeutic applications.

WHAT HAVE BEEN THE BARRIERS TO FAP THERANOSTICS?

A cynical view of the relatively slow pace of therapeutic translation could be that the research environment has changed since the development of PRRT and PSMA RPT, which were developed within academia and leveraged compassionate-use dispensations. This environment removed many of the regulatory hurdles and logistic challenges of running expensive registration trials. By allowing easier access for patients, various institutions generated a considerable, albeit largely retrospective, experience attesting to the efficacy and safety of PRRT (5) and PSMA RPT (6). However, this research model also stifled generation of the evidence base that funding bodies typically require to provide reimbursement. In turn, it created a cottage industry in a small number of academic institutions while simultaneously restricting patient access globally. It was only with the publication of the NETTER-1 (7) and VISION (8) trials and the resulting broader government approvals for these treatments that the pharmaceutical industry became more broadly interested in investing in theranostics at earlier stages of development. This has brought considerable investment into the field and enabled its potential industrialization. Despite these benefits, involvement of the pharmaceutical industry has simultaneously constrained evaluation of novel theranostic agents within formal drug development pathways. These include industry-sponsored phase 1 through 3 clinical trials, a process that is slow and expensive. Nevertheless, within this framework, FAP is such an attractive target that there has been a large and early corporate interest, with licensing agreements for several agents directed against this target. Ongoing clinical trials are in progress in the hope of establishing market approval of these agents for diagnostic and therapeutic use (9).

A more charitable perspective on the slow adoption of FAPI theranostics would be that there are legitimate scientific concerns that have led to cautious clinical translation. These relate to both the pharmacokinetics of some of the early agents that limit the capacity of these agents to deliver meaningful radiation doses to tumor and the biologic features of highly FAP-expressing tumors that are likely to decrease responsiveness to radiation.

PHARMACOKINETIC CONSIDERATIONS

Thus far, successful theranostic paradigms have relied on high radiation dose levels being delivered to tumor sites with acceptable off-target toxicity. The prototypical theranostic approach is ¹³¹I for the treatment of thyroid cancer. A recent report using prospective dosimetry from ¹²⁴I PET/CT in differentiated thyroid cancer indicated that complete response rates are generally achieved only when more than 100 Gy can be delivered to tumor sites (*10*).

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Many years ago, my group at the Peter MacCallum Cancer Centre implemented clinical dosimetry into our radiopharmaceutical therapy program and routinely performed SPECT/CT after each treatment cycle to assess the relationship between tumor radiation dose and response. Recently, we reported a series of 80 neuroendocrine tumor patients receiving PRRT in whom the median cumulative radiation dose over their treatment course was 110 Gy, achieving a 5-y overall survival of 68% but no complete responses (11). We also measured posttreatment dosimetry for [177Lu]Lu-PSMA-617 RPT: patients achieving a prostate-specific antigen response of more than 50% had a median maximum dose to tumor sites of over 50 Gy and a mean dose of around 15 Gy with the first cycle of treatment, making a cumulative dose of between 60 and 100 Gy likely over 4-6 cycles of treatment, but durable complete responses were lacking (12). Rigorous molecular imaging eligibility criteria were used to select patients for both PRRT and PSMA RPT. These criteria included excluding patients with spatially discordant [¹⁸F]FDG-avid lesions lacking the therapeutic target, reasoning that if you cannot see it, you cannot treat it. The relevant diagnostic agents that are used to select patients for PRRT or PSMA RPT typically demonstrate SUVs well above 20 at early time points, and the therapeutic agents have high retention many days later, based on planar or SPECT imaging. Conversely, even in the impressive diagnostic series of [68Ga]Ga-FAPI-04, an agent selected for improved retention relative to [68Ga]Ga-FAPI-02, SUVmax averaged less than 20 in even the tumor types with the highest expression (13). The major exception has been uptake in sarcomas on which FAP is expressed in the neoplastic tumor elements rather than relying on stromal uptake (14).

Although the early monomeric FAPI-based radiopharmaceuticals had fast target accumulation and rapid renal clearance resulting in high-contrast PET images in different cancer types within 10-15 min after intravenous injection, they also demonstrated substantial tumor washout within hours. Although the high tumor-tobackground activity meets the clinical requirements of PET/CT diagnosis, it is conceptionally a disadvantage for radiopharmaceutical therapy. Accordingly, efforts to increase retention of FAPtargeting ligands have been an important priority. From a library of potential agents, the Heidelberg group selected [68Ga]Ga-FAPI-46, which had a longer retention time than the earlier diagnostic agents [68Ga]Ga-FAPI-02 and [68Ga]Ga-FAPI-04 but, like them, was also suitable for labeling with ¹⁷⁷Lu or ⁹⁰Y for therapeutic use. The latter radionuclide has theoretic advantages for FAPI-targeted therapy, with more rapid physical decay being less constrained by tumor clearance of earlier radiopharmaceuticals and a more energetic β-emission providing better tissue penetrance in heterogeneous tumors. The University Hospital Essen group used this agent to treat 21 patients with a range of tumors including both sarcomas and carcinomas. Of importance, these were the only patients from 119 screened who met their eligibility criteria of an $\mathrm{SUV}_{\mathrm{max}}$ of at least 10. These subjects received up to 4 cycles of [90Y]Y-FAPI-46 (15). Disappointingly, only 1 patient achieved a partial RECIST response. The same group subsequently administered 34 (median, 3) cycles of ⁹⁰Y]Y-FAPI-46 to 11 patients with solitary fibrous tumors, which they had chosen as an appropriate proof-of-concept disease group for a prospective evaluation based on diagnostic imaging data indicating very high FAP expression in this neoplasm (16). However, the results were again only modestly successful, with the best response being stable disease in 9 patients (82%).

These results stimulated various radiochemistry groups to adopt various strategies to increase uptake and extend the tumor retention time of FAP-targeting agents. These strategies have included adding an albumin-binding moiety or polyethylene glycol linkers to FAPIbased radiopharmaceuticals to increase circulation time and hence bioavailability; substituting binding motifs with an increased k_{on}/k_{off} profile; modifying linker structures to create more interaction with the extracellular domain of the FAP molecule, particularly through covalent binding; and applying FAP-affine peptides or even monoclonal antibodies instead of small-molecule inhibitors.

Most of the agents developed using these strategies have been described primarily in preclinical studies. Fu et al. evaluated the therapeutic potential of one of the few agents to enter a clinical therapy trial, [¹⁷⁷Lu]Lu-EB-FAPI (LNC1004), which is a FAP ligand modified by addition of Evans blue to increase circulation time and hence bioavailability through albumin binding (*17*). This first-in-human, prospective clinical trial included patients with metastatic thyroid cancer refractory to ¹³¹I treatment or resistant to tyrosine kinase inhibitors. Imaging revealed prolonged tumor retention, which resulted in relatively high mean absorbed tumor doses (8.50 ± 12.36 Gy/GBq). The mean effective half-life for tumor lesions was 92.46 ± 9.66 h, which is an improvement on prior monomeric agents but still shorter than the physical half-life of ¹⁷⁷Lu. Nevertheless, encouragingly, the objective RECIST response and disease control rates were 25% and 83%, respectively.

Improved targeting and retention have also been evaluated through use of homodimers that contain 2 FAP-binding motifs. In a pilot human study, the dimer was shown to have delivered approximately 10-fold higher absorbed doses to lesions (a median of 6.70 [interquartile range, 3.40–49] Gy/GBq dose per cycle) than does the monomer, used as a comparator. This agent, [¹⁷⁷Lu]Lu-DOTAGA.(SA.FAPi)2, has now been investigated for therapeutic effectiveness and safety in breast cancer patients (*18*). Although treatment protocols varied and responses were limited to 16 of the 19 patients treated, the results were promising, with molecular imaging responses observed during and after treatment.

In the hope that a peptide-based FAP ligand might perform better than monomeric FAP agents, [177 Lu]Lu-FAP-2286 was evaluated for treatment in 11 patients with advanced adenocarcinomas of the pancreas, breast, rectum, or ovary (*19*). Although an acceptable safety profile was demonstrated, the only positive clinical outcome was an improvement in pain in 3 patients. The doses obtained in bone metastases were 3.0 ± 2.7 Gy/GBq (range, 0.5-10.6 Gy/GBq). [177 Lu]Lu-FAP-2286 is being pursued through the ongoing phase I/II LuMIERE trial (NCT04939610). Further modifications on this peptide that have enhanced its pharmacokinetic properties have produced an agent called 3BP-3940 that has entered clinical trials in Germany.

Attempts to improve tumor retention by creating a heterodimer targeting both FAP and other cell-surface targets have also been described but not yet translated into human therapy trials. One such agent, FAPI-RGD (LNC1007), which combines FAPI-02 and cyclic RGD, targeting the integrin $\alpha_{v}\beta_{3}$, which is known for its role in angiogenesis and cell migration, has been labeled with both ⁶⁸Ga and ¹⁸F and is suitable for ¹⁷⁷Lu labeling.

Despite these promising advances, it remains to be proven whether these or other radiochemistry advances will allow sufficient radiation doses to be delivered within clinically feasible treatment protocols. Critical to this question is the biology associated with high FAP expression.

BIOLOGIC CONSIDERATIONS

Nonmalignant cells within the tumor microenvironment, including immune cells, neovessels, and cancer-associated fibroblasts (CAFs), are now recognized as important modulators of both cancer progression and therapeutic response. These comprise the stromal compartment, which also includes noncellular elements, an important component of which is the extracellular matrix (ECM). CAFs are the primary cell responsible for deposition and remodeling of the ECM and particularly for collagen formation, which is a feature of desmoplastic tumors. Through inefficient perfusion, hypoxia is likely to be prevalent in such tumors and is an important mediator of radioresistance through several mechanisms including failure of apoptosis, enhanced DNA repair and activation of autophagy (20). Accordingly, tumors that have high FAP expression may require even higher radiation doses than those with low expression. This may justify consideration of combining FAP-targeting theranostic agents with radiosensitizing therapies. These potentially include chemotherapy, especially those that already have single-agent efficacy in the given tumor, and agents that modify DNA repair.

Additionally, at a microscopic level, irradiation of the epithelial components of the tumor relies primarily on crossfire effects from CAFs. This might argue for more energetic β-particle emitters than α -emitters, which might selectively depopulate CAFs. Although this might be advantageous for tumor control, recently it has also become clear that there is a complex interplay of CAFs and immune cells that can both suppress and accelerate tumor growth. This is likely to be driven by the significant biologic heterogeneity that has been identified in CAF subtypes both within and between cancers (21). As yet, little is known about how the various stromal and epithelial elements might respond to radiation delivered via CAFs. Being radiosensitive, resident lymphocyte populations might be more susceptible than tumor-associated macrophages, for example. This might tip the balance to a more immunosuppressive tumor microenvironment. Conversely, through damaging cells without necessarily killing them, it may be possible to promote neoantigen expression and immune recognition within previously immunosuppressed tumors. Evaluation of combinations of radiopharmaceutical therapy with immune checkpoint inhibitors is a logical consequence of such considerations.

WHERE TO FROM HERE?

While awaiting the results of single-agent therapeutic trials, the nuclear medicine community needs to work closely with scientists and clinicians with expertise in CAF and tumor microenvironment biology to logically design clinical trials that address the challenges posed by desmoplastic tumor types. In my opinion, it is both naïve and arrogant to believe that we will emulate the curative capability of radioiodine therapy of differentiated thyroid cancer, or even the effective palliation provided by PRRT or PSMA RPT, without effective combination therapies, which may even include combining radiopharmaceutical therapies. Still, it is happening and will continue to do so for years to come.

DISCLOSURE

Rodney Hicks is a scientific advisor to, and shareholder in, Telix Pharmaceuticals. He receives research funding from LNC Pharma and precursor supply from Sofie for FAPI-46 for an Australian Medical Research Future Fund grant (APP 1200038) investigating diagnostic FAPI agents. He is founder and the major shareholder of PreMIT Pty Ltd., a research and development company involved in developing novel theranostic agents. No other potential conflict of interest relevant to this article was reported.

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REFERENCES

- Haberkorn U, Altmann A, Giesel FL, Kratochwil C. 1,090 publications and 5 years later: is FAP-targeted theranostics really happening? J Nucl Med. 2024;65:1518–1520.
- Hicks RJ, Roselt PJ, Kallur KG, Tothill RW, Mileshkin L. FAPI PET/CT: will it end the hegemony of ¹⁸F-FDG in oncology? J Nucl Med. 2021;62:296–302.
- Lindner T, Loktev A, Altmann A, et al. Development of quinoline-based theranostic ligands for the targeting of fibroblast activation protein. *J Nucl Med.* 2018;59: 1415–1422.
- Sollini M, Kirienko M, Gelardi F, Fiz F, Gozzi N, Chiti A. State-of-the-art of FAPI-PET imaging: a systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging*. 2021;48:4396–4414.
- Hicks RJ, Kwekkeboom DJ, Krenning E, et al.; Antibes Consensus Conference participants. ENETS consensus guidelines for the standards of care in neuroendocrine neoplasia: peptide receptor radionuclide therapy with radiolabeled somatostatin analogues. *Neuroendocrinology*. 2017;105:295–309.
- Kratochwil C, Fendler WP, Eiber M, et al. EANM procedure guidelines for radionuclide therapy with ¹⁷⁷Lu-labeled PSMA-ligands (¹⁷⁷Lu-PSMA-RLT). *Eur J Nucl Med Mol Imaging*. 2019;46:2536–2544.
- Strosberg J, El-Haddad G, Wolin E, et al.; NETTER-1 Trial Investigators. Phase 3 trial of ¹⁷⁷Lu-Dotatate for midgut neuroendocrine tumors. *N Engl J Med.* 2017; 376:125–135.
- Sartor O, de Bono J, Chi KN, et al.; VISION Investigators. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med. 2021;385:1091–1103.
- Mosessian S, Jensen JD, Enke AS. Current state of clinical trials and regulatory approvals with fibroblast activation protein targeting interventions. *PET Clin.* 2023;18:429–439.
- Plyku D, Hobbs RF, Wu D, Garcia C, Sgouros G, Van Nostrand D. I-124 PET/CT image-based dosimetry in patients with differentiated thyroid cancer treated with I-131: correlation of patient-specific lesional dosimetry to treatment response. *Ann Nucl Med.* 2022;36:213–223.
- 11. Alipour R, Jackson P, Bressel M, et al. The relationship between tumour dosimetry, response, and overall survival in patients with unresectable neuroendocrine neoplasms (NEN) treated with ¹⁷⁷Lu DOTATATE (LuTate). *Eur J Nucl Med Mol Imaging*, 2023;50:2997–3010.
- Violet J, Jackson P, Ferdinandus J, et al. Dosimetry of Lu-177 PSMA-617 in metastatic castration-resistant prostate cancer: correlations between pre-therapeutic imaging and "whole body" tumor dosimetry with treatment outcomes. *J Nucl Med.* 2019;60:517–523.
- Kratochwil C, Flechsig P, Lindner T, et al. Ga-FAPI PET/CT: tracer uptake in 28 different kinds of cancer. J Nucl Med. 2019;60:801–805.
- Kessler L, Ferdinandus J, Hirmas N, et al. ⁶⁸Ga-FAPI as a diagnostic tool in sarcoma: data from the ⁶⁸Ga-FAPI PET prospective observational trial. *J Nucl Med.* 2022;63:89–95.
- Fendler WP, Pabst KM, Kessler L, et al. Safety and efficacy of ⁹⁰Y-FAPI-46 radioligand therapy in patients with advanced sarcoma and other cancer entities. *Clin Cancer Res.* 2022;28:4346–4353.
- Hamacher R, Pabst KM, Cheung PF, et al. Fibroblast activation protein α-directed imaging and therapy of solitary fibrous tumor. J Nucl Med. 2024;65:252–257.
- Fu H, Huang J, Zhao T, et al. Fibroblast activation protein-targeted radioligand therapy with ¹⁷⁷Lu-EB-FAPI for metastatic radioiodine-refractory thyroid cancer: first-in-human, dose-escalation study. *Clin Cancer Res.* 2023;29:4740–4750.
- Yadav MP, Ballal S, Martin M, et al. Therapeutic potential of [¹⁷⁷Lu]Lu-DOTAGA-FAPi dimers in metastatic breast cancer patients with limited treatment options: efficacy and safety assessment. *Eur J Nucl Med Mol Imaging*. 2024;51:805–819.
- Baum RP, Schuchardt C, Singh A, et al. Feasibility, biodistribution, and preliminary dosimetry in peptide-targeted radionuclide therapy of diverse adenocarcinomas using ¹⁷⁷Lu-FAP-2286: first-in-humans results. *J Nucl Med.* 2022;63:415–423.
- Hill RM, Fok M, Grundy G, Parsons JL, Rocha S. The role of autophagy in hypoxia-induced radioresistance. *Radiother Oncol.* 2023;189:109951.
- Chen X, Song E. Turning foes to friends: targeting cancer-associated fibroblasts. Nat Rev Drug Discov. 2019;18:99–115.