FAP: The Next Billion Dollar Nuclear Theranostics Target?

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The recent successful clinical translation of nuclear theranostics (*1,2*) fueled industry investment in the radiopharmaceutical market (*3*). Among other examples, Novartis invested $6 billion to acquire Endocyte (^{177}Lu-PSMA-617) and Advanced Accelerator Applications (AAA; ^{177}Lu-DOTATATE [Lutathera]) and Bracco S.p.A. obtained Blue Earth Diagnostics (radiohybrid PSMA [prostate-specific membrane antigen]-targeted technology) for $500 million. Thus, investors have recognized the potential clinical benefits and substantial financial upside of nuclear theranostics and are now in hot pursuit of the next relevant nuclear theranostics target. Fibroblast activation protein (FAP) has emerged as the frontrunner, and the next gold rush appears to be around the corner.

WHY IS FAP A PROMISING TARGET?

FAP, also known as seprase or prolyl-endopeptidase-FAP, is a type II membrane-bound glycoprotein enzyme with peptidase activity (substrates can be, among others, gelatin or collagen). FAP is highly expressed on the cell surface of activated but not quiescent fibroblasts (*4,5*). Expression in normal adult tissues is absent or low (*6*). Expression increases in remodeling processes such as wound healing, inflammation, or fibrosis when fibroblasts become activated (*7*). Importantly FAP is highly expressed by cancer-associated fibroblasts (CAFs), a major constituent of tumor stroma (*4,7,8*).

WHAT ARE CAFS?

Tumor masses consist of cancer cells but also vascular structures, inflammatory cells, fibroblasts, and collagen that together make up the tumor stroma that can account for up to 90% of the mass in highly desmoplastic cancers (*4,7,8*). Cancer cells induce the fibroblast activation via TGFbeta. CAFs have a supporting function on cancer growth and invasion. They contribute to the remodeling of the extracellular matrix (collagenolysis) and promote invasiveness and angiogenesis and, via growth factors and cytokine secretion, can induce epithelial to mesenchymal transition (*6*). CAFs are also involved in the immunologic interactions between the tumor and the host (*9*).

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WHY IS FAP-TARGETED THERAPY ATTRACTIVE?

FAP-positive CAFs are found in more than 90% of epithelial cancers, therefore representing a potential pan-cancer target (*6*). Targeting FAP to deplete stromal CAFs may disrupt cancer-supportive functions and inhibit cancer growth (*10–12*). Furthermore, by breaking the stroma barrier, the effectiveness of other pharmacologic, immunologic, radiation- or cell-based systemic therapies may thus be enhanced (*4–6*).

FAP-targeted molecular radiotherapy (MRT) can deliver ionizing radiation to CAFs directly and also to cancer cells, via crossfire effects. Combining α- and β-emitters may improve these dual antitumor effects via short-range α-radiation to CAFs and mid- to long-range β-radiation to cancer cells. As another potential application, combining FAP-targeted with PSMA-targeted MRT may increase radiation doses in stroma-rich prostate cancer lesions (*13,14*).

WHY IS FAP-TARGETED IMAGING ATTRACTIVE?

Tumor lesions exceeding 1–2 mm in size require the formation of a supporting stroma (*15*). As stroma volume can be larger than cancer cell volume, stroma-targeted PET imaging may be more sensitive than glucose metabolic PET imaging for detecting small lesions if FAP is expressed sufficiently (Fig. 1). FAP-targeted PET [Fig. 1] imaging may also be attractive for detecting tumor lesions with low or heterogeneous glucose metabolism or those located in close vicinity to highly glycolytic normal tissues (*16–18*). Additional potential advantages include early imaging at 10 min after injection and the absence of required fasting. Finally and most importantly, FAP-targeted PET imaging could serve as a precise predictive biomarker of response to any FAP-targeted treatments across most cancers.

As a limitation, FAP expression is not cancer-specific due to its expression in many tissue-remodeling processes. This may, for instance, render the differentiation between chronic pancreatitis and pancreatic ductal adenocarcinoma difficult (*19*). Conversely, FAP-targeted PET imaging may be useful for many non-oncologic imaging applications such as myocardial infarction (*20–22*), chronic inflammatory diseases (*23*), and lung, liver or kidney fibrosis (*24*).

FAP-TARGETED RADIOPHARMACEUTICALS

Molecular Imaging

The Heidelberg group has recently developed quinolone-based FAP inhibitors (FAPI) with a DOTA-chelator moiety to enable radiolabeling. One early derivative, FAPI-02, was near completely internalized after 1 h of incubation. First-in-human PET/CT studies of ^{68}Ga-FAPI-02 PET/CT scans demonstrated high-contrast tumor imaging across various cancers (Fig. 1) (*7,16,25*). To optimize

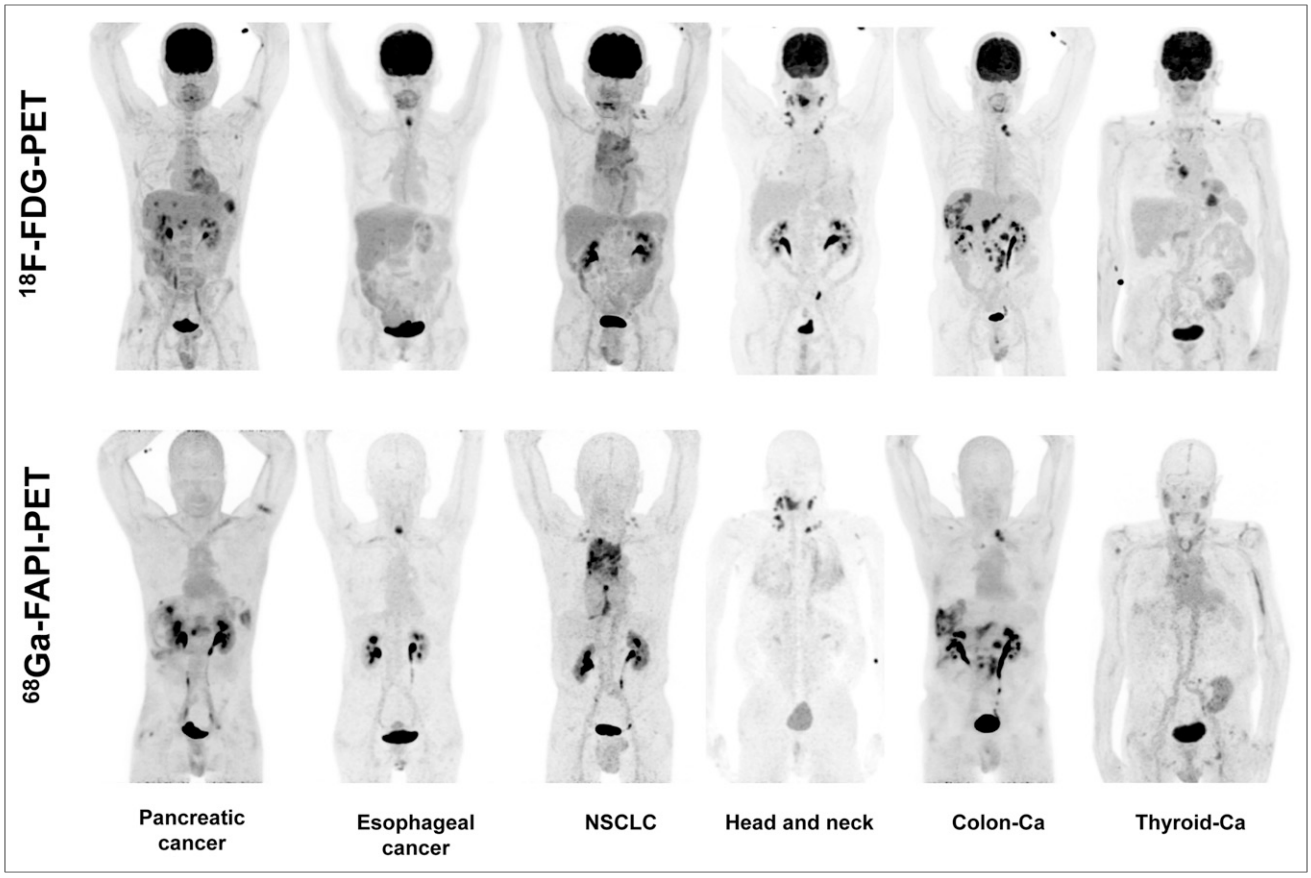

FIGURE 1. ^{68}Ga-FAPI and ^{18}F-FDG PET images in patients with various cancers. (Reprinted with permission of (*16*).)

tracer uptake and retention, a series of subsequent derivatives was developed (*25*). ^{68}Ga-FAPI-04 showed the most favorable properties for PET imaging (low nanomolar affinity to FAP, near-complete internalization of radioactivity bound to FAP, and rapid blood clearance) with impressive lesion-to-background ratios in patients with a broad range of cancers (*26*). ^{18}F-labeled compounds (FAPI-74, RPS-301) are being developed to improve potential commercial distribution (*27–29*).

Molecular Radiotherapy

Although imaging probes are clinically highly relevant, the market interest arises from potential therapeutic applications that generate an order of magnitude greater return on investment. There is no published report of FAP-targeted MRT except a single case of a late-stage breast cancer patient with bone metastases treated with ^{90}Y-labeled FAPI-04 (*25*). A single administration of 2.9 GBq of ^{90}Y-FAPI-04 led to symptomatic improvement without significant toxicity. However, further optimization steps are needed. For instance, the physical half-life of the therapeutic isotope needs to be matched to the tumor retention time. FAPI-04 clears relatively rapidly from tumor tissue, limiting the achievable radiation dose delivery. A therapeutic isotope with a shorter physical half-life may be more effective than ^{90}Y. The radiation type (α vs. β) also requires optimization. In a preclinical study, a single administration of ^{225}Ac-FAPI-04 resulted in tumor growth retardation in mice bearing PANC-1 xenografts (*30*).

Further modifications to the FAPI compounds were performed to improve tumor retention while retaining the imaging contrast obtained with FAPI-02 and FAPI-04 (*6,17,31*). A further increase of tumor retention time was achieved with FAPI-46 (*17,31*). ^{68}Ga-FAPI-46 PET/CT imaging had a favorable dosimetry profile and showed high tumor-to-background ratios increasing over time, suggesting more favorable kinetics for potential therapeutic applications (*31*).

IS THE INDUSTRY INVESTING IN FAP-TARGETED NUCLEAR THERANOSTICS?

3B-Pharmaceuticals developed a new class of FAP-targeted radiolabeled peptidomimetics (FAP-3BP-2286) that have been licensed to Clovis Oncology for $12 million. Sofie Biosciences, Inc. (SOFIE) signed a $5 million exclusive global license agreement with the University of Heidelberg for the small-molecule FAPI compounds. Both companies are planning to file investigational new drug applications for their FAP-targeted radiopharmaceuticals in 2020. Even when no diagnostic or therapeutic data are yet available, these acquisitions underscore the high industry interest in FAP-targeted nuclear theranostics compounds.

Challenges

To streamline research and development of FAP-targeted compounds, the nuclear medicine community (industry and academia) can learn from the National Oncologic PET Registry successes for FDG and the successful translation of ^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, ^{18}F-fluciclovine, and, more recently, the PSMA imaging agents. Strategies for translating FAP-targeted imaging agents may range from phase 3 diagnostic efficacy studies for each cancer

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type to pan-cancer diagnostic or predictive biomarker applications, respectively. Prospective exploratory studies have been registered and initiated (NCT04147494).

The effectiveness of FAP-targeted MRT is also unknown, and it may not be sufficiently effective as a single agent. Thus, combination therapy approaches including, among others, immunotherapy and MRT with α-/β-combination or multitargeted MRT should be a priority for research at least in preclinical models.

In summary, FAP is a promising target for imaging and therapy. Industry has embraced nuclear theranostics targeting FAP. The next gold rush has begun early.

DISCLOSURE

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