9.1 FAPI and beyond

M. Vorster, M. Sathekge

DOI: 10.60994/NUM202325

INTRODUCTION

Infective diseases (i.e. TB, HIV and malaria) remain a significant contributor to mortality and morbidity worldwide and inflammatory processes underly various important chronic and debilitation diseases with a similar impact on global morbidity and mortality[1]. The ability to make an early, accurate and non-invasive diagnosis, and to detect extent of disease involvement, forms an important part of patient management. PET/CT imaging provides this as a single whole-body diagnostic tool that has the added ability to predict, prognosticate and to monitor treatment response.

Generator-based PET tracers, such as those based on Gallium-68 provide attractive PET tracer possibilities that bypass the need for a nearby-cyclotron (with its associated costs and logistics), are versatile and cost-effective. Gallium-68 can be linked via several chelators (i.e. DOTA, NOTA, NODAGA and TRAP) to image the various targets that are provided by infective and inflammation role players such as antibodies, receptors on white blood cells, selectins, integrins, chemokines, folate receptors, anti-microbial proteins, peptides and siderophores[2] (Fig. 1).

Some of the potential additional advantages of using Ga-68 based tracers over the more widely used [^{18}F]FDG, includes improved specificity, improved distinction between infection and inflammation and improved bio-distribution in areas such as the brain and heart[2].

The aim of this chapter is to summarize some of the most prominent work done with Gallium-68-based tracers, with emphasis on ^{68}Ga-fibroblast activation protein inhibitors (^{68}Ga-FAPI) in the settings of infection and inflammation. The focus is on tracers that have already been used in humans (Table 1), and particularly on the organ systems that are most affected by infective- and inflammatory processes (i.e. lungs, cardiovascular- and musculoskeletal systems).

FIBROBLAST ACTIVATION PROTEIN (FAP) AS AN INFECTION AND INFLAMMATION IMAGING AGENT

Fibroblast Activation Protein (FAP) is a type II membrane-bound glycoprotein and a serine protease classified in the dipeptidyl peptidase 4 (DPP4) family[3]. It is overexpressed in cancer-associated fibroblasts and in

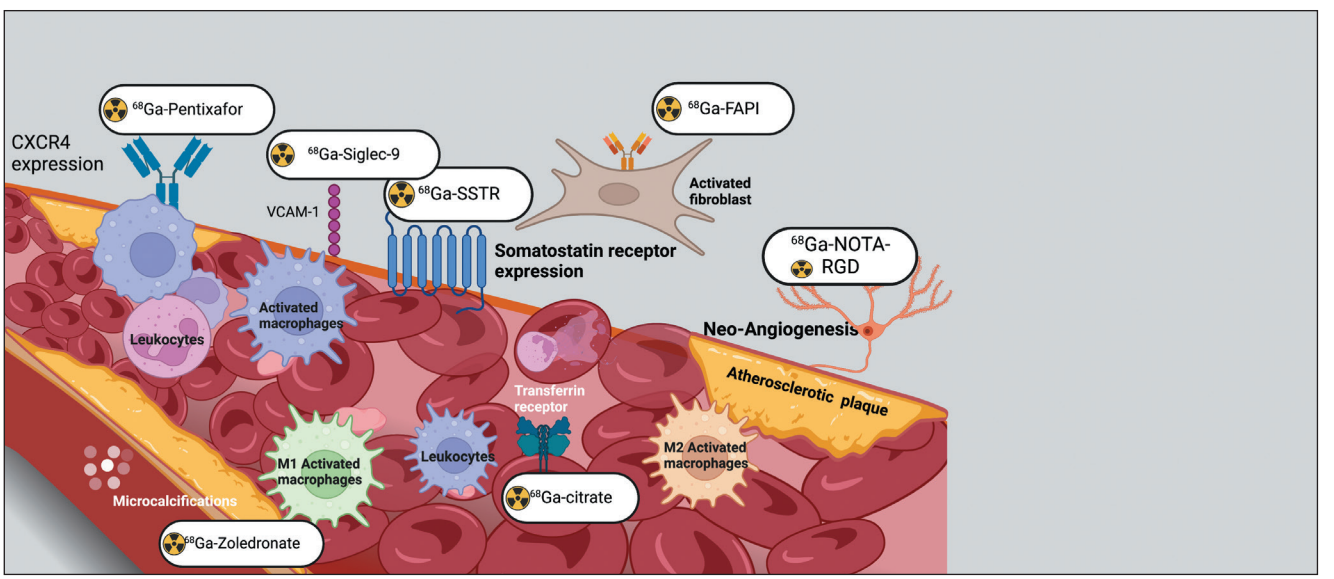


Figure 1. Important pathophysiological targets in infection and inflammation imaging.

Table 1. PET tracers and targets clinically used in infection and inflammation imaging

PET tracer	Pathophysiological target	Clinical Application (s)
^{68}Ga-FAPI	FAP on activated fibroblasts	Atherosclerosis, MI, cardiac remodelling, IPF, tumour-associated inflammation, SLE
^{68}Ga-NOTA/DOTA-RGD	$\alpha v\beta 3$ Integrins, neo-angiogenesis	Atherosclerosis, auto-immune diseases
^{68}Ga-DOTA-TATE/TOC/NOC	Somatostatin receptor expression on activated leukocytes	Atherosclerosis, vulnerable plaque, auto-immune diseases
^{68}Ga-CXCR4	CXCR4 receptor expression on immune cells	Atherosclerotic plaques, myocardial infarct, cerebral infarct, remodelling, theranostic approaches
^{68}Ga-citrate	Transferrin receptors, ferritin, lactoferrin	Atherosclerosis, sarcoidosis, IBD, Lower limb prosthesis
^{68}Ga-DOTA-Siglec-9	Vascular adhesion protein 1	Rheumatoid arthritis, Synovitis
^{68}Ga-NODAGA-Zoledronate	Calcifications	Atherosclerotic plaques

activated fibroblasts that are involved in wound healing and inflammation, in fibrosis, arthritis, and atherosclerotic plaques. Various radiolabelled quinolone-based tracers that act as FAP inhibitors (FAPI) have now successfully been used as PET tracers. The application of these FAPI tracers has now been well validated in oncology with the emergence of several recent systematic reviews and meta-analysis[4-7].

Entering the keywords "FAP/FAPI + inflammation/ infection imaging" into Google Scholar, results in 649 results for any period. Changing the selected period to 2019 onwards, results in 392 results and narrowing the search further to 2023, results in 103 publications. This gives an idea of the explosion of FAPI-related publications in settings outside of oncology over the past 5 years (60 % of current publications happened within less than 5 years). To date FAPI has been investigated in the mostly in the non-oncological settings of musculoskeletal pathology (degenerative, trauma, joint-disease and infected prosthesis) cardiovascular disease (eg post-MI, cardiac failure, atherosclerosis), auto-immune diseases (RA, IgG4-related disease and systemic lupus erythematosus) and infective diseases like TB and COVID-19[5,7]. In a recent editorial by Treglia and Albano[8], the authors comment that the scientific community is "watching it (FAPI tracers) like a hawk". They also provide a useful summary of some of the largest FAPI-based studies performed in non-malignant settings[9].

Why is there such an interest in FAPI as an infection and inflammation image? It is not difficult to see the resemblances to FDG, which has served nuclear medicine physicians well with its versatility (often criticized as non-specificity!) as an oncology-, infection- and inflammation imaging agent. Unlike FDG, however, it enables in-house labelling, generator-based PET imaging, as well as possibilities for SPECT/CT imaging exist. This obviates the need for a nearby cyclotron, with resultant cost, logistics and patient scheduling advantages. In addition, no specific patient preparation is needed, normal biodistribution allows detection of pathology in the brain, liver, gastrointestinal and genitourinary tracts with good target to background ratios. The cherry on top is provided by the theranostic potential[10].

Several systematic reviews and meta-analyses have also started to appear on the use of FAPI in benign or non-malignant settings[5,7,11]. A recent systematic review by Windisch[11] and colleagues highlighted and summarized some of the evidence accumulated so far on the use of FAPI PET for non-malignant indications. In a 2023 "expedited systematic review" on non-malignant findings on FAPI PET by Bentestuen et al.[5].

All the afore-mentioned reviews, systematic reviews, and meta-analyses comment on the suboptimal levels of evidence provided by small non-standardised cohorts of patients and case reports and emphasize the need for bigger, standardized prospective studies to create high levels of evidence to support these non-oncological indications for FAPI PET. In addition, histological, clinical and/or radiological confirmation of FAPI-avid lesions will be important to determine false positive findings. Confirmation of differences in tracer kinetics between benign and malignant lesions is also needed.

CARDIOVASCULAR SYSTEM INFECTION AND INFLAMMATION IMAGING

A particular area of interest, with mounting evidence, is the application of FAPI in cardiovascular diseases[12]. ^{68}Ga-FAPI-PET imaging, in this setting, is based on the rationale that FAP is overexpressed in inflamed tissue and during the process of tissue re-modelling. This makes for attractive applications in the imaging of atherosclerosis, ischemia, myocardial infarction, post-infarct remodelling of the left ventricle and in cardiac failure. Cardiac sarcoidosis, atherosclerosis, infarction, cardiac failure represents important clinical problems that require early detection and risk stratification. A 2023 overview by Caobelli and Nappi[12] highlights some of the recent advances and applications of FAPI in cardiovascular disease and provides a summary of ongoing clinical trials which may produce interesting findings for future applications.

Abnormal cardiac accumulation of FAPI has been documented in association with a history of radiation to the chest, with overweight and obesity, as well as with

diabetes mellitus and cardiotoxicity. Several investigators have highlighted its integral role in the remodelling of infarcted tissue, also in the right ventricles of patients that suffer from pulmonary hypertension[13].

Several studies (both pre-clinical and clinical) have demonstrated increased FAPI accumulation in myocardial infarction[14,15]. This FAPI expression exceeded the area affected by the infarction (as demonstrated on MR), but importantly, it corresponded to the degree of ventricular dysfunction during follow up. It appears that activated fibroblasts tend to persist for longer (even up to 12 months) and has a detrimental effect on cardiac function[16]. Imaging these processes may provide important prognostic information. Significant FAPI uptake has also been linked to 5-year risk of sudden cardiac death in patients with hypertrophic cardiomyopathy. The application of FAPI PET in the settings of myocardial infarct, remodelling, myocarditis, heart failure and prognostication is likely to be among the most valuable[13,17,18].

^{68}Ga-CXCR4 PET imaging has also been used in this clinical setting based on its integral role in inflammation and in the recruitment and homing of stem-and progenitor cells to the infarct zone[16,19,20]. ^{68}Ga-CXCR4 PET imaging provides a high signal intensity in atherosclerotic plaques compared to the low background signal in the arterial wall. It has a favourable biodistribution (uptake in the spleen, adrenals, and bone marrow) with no need for any special patient preparation and its potential role in the evaluation of atherosclerotic plaques has now been investigated by several groups. Other applications include imaging of myocardial- and cerebral infarcts, tissue remodelling and the potential of theranostic approaches in auto-immune diseases[21,22] (Fig. 2).

Integrins such as αvβ3 is over-expressed in newly formed vasculature and on CD 68+ macrophages, which can be imaged with ^{68}Ga-RGD PET. Over-expression of integrin αvβ3 enables imaging of neo-vascularisation, atherosclerosis, and plaques in cardiovascular disease[23]. Other Ga-68-based tracers that have been used in these settings with varying levels of success, include Galuminox[24], ^{68}Ga-Zoledronate[25], ^{68}Ga-MSA, and ^{68}Ga-DOTA-nitroimidazole.

Non-invasive detection of cardiac sarcoidosis remains an important aim, considering its significant morbidity and mortality. Several studies have now demonstrated the value of ^{68}Ga-SSTR imaging for this application in targeting the overexpression of SSTR-2 on sarcoid granulomas[26-28]. Added advantages include the absence of normal tracer bio-distribution in the heart, the absence of patient preparation, and the possibility of differentiating between inflammation and fibrosis[26,29].

Somatostatin receptor-based imaging has also played a prominent role in the imaging of atherosclerosis, plaques, myocarditis, ischemia and myocardial infarction[28,30-32].

Much of the currently available evidence is still preliminary, but appears quite promising, and FAPI-based imaging is likely to outperform the other Ga-68-based tracers that have been applied in this setting.

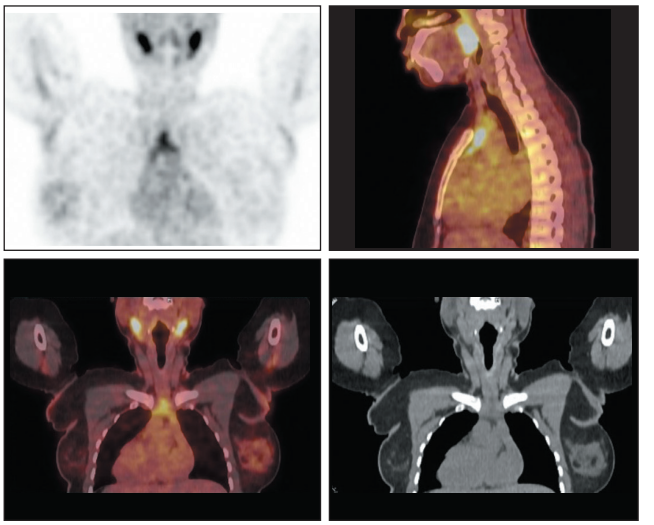


Figure 2. Demonstrates intense thymus uptake on ^{68}Ga-CXCR4 PET in a patient with advanced breast cancer.

PULMONARY INFECTIONS AND INFLAMMATION

Interstitial lung diseases (ILD) comprise a spectrum of lung pathology that are characterized by inflammation and/ or fibrosis, and which ultimately result in respiratory difficulty- or failure. The ability to diagnose these conditions at an early stage and to monitor treatment response, could significantly alter current morbidity and mortality[33].

In a first-in-human study, Christina Bergmann[34] and colleagues provided results to support that fibroblast activation correlates with both lung fibrotic activity and with progression of disease in patients with systemic sclerosis-associated ILD. The authors further suggested that ^{68}Ga-FAPI-04 PET-CT might improve risk assessment of systemic sclerosis-associated ILD. They enrolled 21 patients with systemic sclerosis-associated ILD confirmed by high-resolution CT (HRCT) and 21 healthy controls. All participants were imaged with ^{68}Ga-FAPI-04 PET-CT and underwent standard-of-care procedures, that included HRCT and lung function tests. Baselines studies were obtained in all, and follow-up studies were performed in a subgroup of patients that were treated with nintedanib at 6-10 months. Significantly higher tracer accumulation demonstrated in those ILD patients with extensive disease or with previous progression. Higher ^{68}Ga-FAPI-04 uptake at baseline was an independent indicator of disease progression, and changes in serial ^{68}Ga-FAPI-04 uptake values corresponded to the observed treatment response to nintedanib[34].

Hao and colleagues[35] reported on a 53 yr. old patient with confirmed TB meningitis who was imaged with both

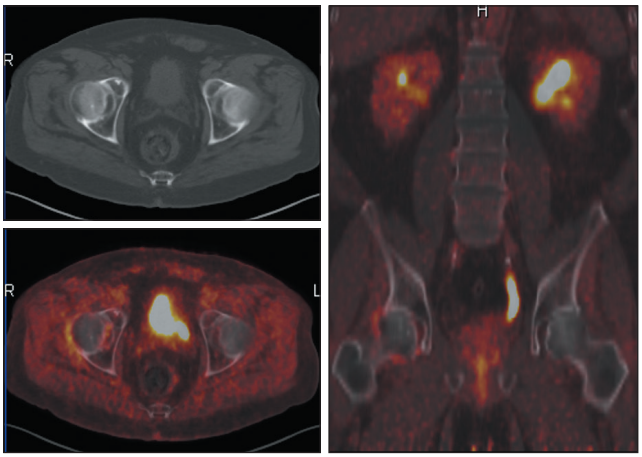


Figure 3. Demonstrates FAPI-46 uptake in an osteoporotic hip.

[^{18}F]FDG- and ^{68}Ga-DOTA-FAPI-04 PET/CT. The [^{18}F]FDG PET/CT was performed after cerebrospinal fluid confirmation of Mycobacteria Tuberculosis growth to evaluate the extent of disease involvement. Due to the significant interference of normal tracer bio-distribution on FDG PET, no brain lesions could be visualized. A subsequent ^{68}Ga-DOTA-FAPI-04 PET/CT study, however, confirmed several lesions in the brain, which corresponded to the pathology reported on MR. Additionally, lung- and spinal involvement was clearly demonstrated, which was not visible on the [^{18}F]FDG PET/CT study. Another case study by Zhao and colleagues demonstrated ^{68}Ga-FAPI uptake in a confirmed pulmonary cryptococcal infection. These two cases point to the possible application of ^{68}Ga-FAPI in imaging of TB and fungal infections in the lung[36].

Sviridenko et al. imaged six post-Covid patients with both FDG and ^{68}Ga-FAPI-46 for suspected lung fibrosis and compared them to 9 healthy controls. Significant ^{68}Ga-FAPI was present in all areas with lung fibrosis, whilst no significant FDG accumulation was detected. The authors suggested that ^{68}Ga-FAPI-46 PET/CT may play an important complimentary role in the early diagnosis of long-term fibrotic changes after severe respiratory infections such as COVID-19[37].

Other ^{68}Ga-based tracers that have been applied in lung infections and/ or inflammation (with varying levels of success), include ^{68}Ga-nitroimidazole[38], ^{68}Ga-Siglec9[39] and ^{68}Ga-citrate[40,41].

MUSCULOSKELETAL INFECTIONS AND INFLAMMATION

Several investigators have evaluated the use of ^{68}Ga-citrate PET in clinically proven or suspected prosthetic hip/knee joint infections. Tseng and colleagues suggested a possible complimentary role of citrate to FDG PET in patients with prosthetic joints as a possible better discriminator between inflammation and infection.

Xu et al. compared the use of ^{68}Ga-citrate PET in 39 patients with suspected prosthesis complications to image findings on three-phase bone scintigraphy and SPECT/CT and suggested that ^{68}Ga-citrate PET may distinguish aseptic loosening from joint infection[42].

An early and accurate diagnosis of per-prosthetic infection and / or loosening is integral to preventing the potential devastating consequences to these patients. Currently, available nuclear medicine studies all suffer from various limitations (cumbersome logistics with the need for multiple studies and patient preparation, complicated diagnostic criteria, etc), which could potentially be addressed by imaging with ^{68}Ga-FAPI. Loosening of the prosthesis results in the formation of a membrane, and infective processes are accompanied by activated fibroblasts. This makes imaging with ^{68}Ga-FAPI feasible.

Wang et al.[43,44] presented a case series consisting of four symptomatic patients post total hip arthroplasty that were imaged with ^{68}Ga-FAPI-PET. The gold standard was provided by histological confirmation, and the researchers concluded that in addition to providing an accurate diagnosis, further information was provided in confirmation of the site and the extent of involvement. The authors report on two distinctly different patterns of tracer accumulation in this small case series: low intensity, linear uptake between the bone and the prosthesis in loosening, compared to high intensity, diffuse uptake noted in infection[44].

In a larger follow-up study by the same group[43], 103 symptomatic patients post hip arthroplasty were included and imaged with ^{68}Ga-DOTA-FAPI-04. This followed their pre-clinical studies on rabbit models with infection and loosening, in which ^{68}Ga-FAPI was found to be superior to FDG. The researchers used the 2018 Evidence-Based and Validation Criteria as their reference standard and a diagnosis of peri-prosthetic joint infection was based on two diagnostic criteria, the tracer uptake pattern and SUVmax, which was present in 28 patients. The following impressive results were reported: regarding the SUVmax, the area under the curve approached 90 % (which was superior to serological tests). Employing a SUVmax cut-off value of 7.53 resulted in a sensitivity of 100 % and a specificity of 72 %. Considering the uptake patterns, 100 % sensitivity, 93.1 % specificity and 95 % accuracy were reported, and on radiomics analysis, the features of infected prosthesis were significantly different from those of loosening. These impressive results are very promising for the use of ^{68}Ga-DOTA-FAPI-04 PET/CT in distinguishing prosthetic joint infection from loosening[43] (Fig. 3).

AUTO-IMMUNE DISEASES

Aiming to separate fibrosis from inflammation, Scmidkonz[45] and colleagues included and analysed 27

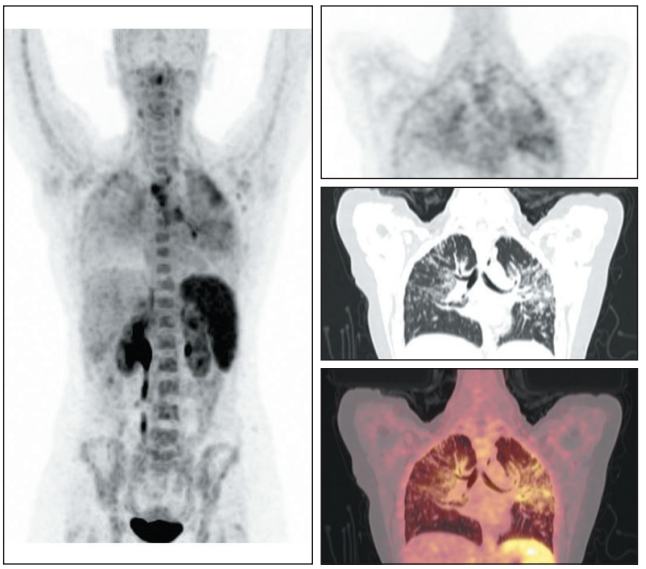


Figure 4. Demonstrates Pentixafor uptake in the lungs of a patient with sarcoidosis.

patients with inflammatory, fibrotic, and overlapping manifestations of IgG4-related disease with PET/CT imaging. Study participants were imaged with [^{18}F]FDG and ^{68}Ga-FAPI-04 PET/CT before and after immunosuppressive treatment and image findings were correlated to clinical, MR, and histopathology data.

The two PET tracers demonstrated incongruent patterns of uptake, and based on the additional clinical-, imaging- and histology data, the authors concluded that ^{68}Ga-FAPI imaging better differentiated fibrosis from inflammatory changes. This finding could potentially translate into more individualized patient treatment approaches. Luo et al.[46] presented similar results in their study consisting of 26 patients with IgG4-Rd who were imaged with both of the afore-mentioned tracers. ^{68}Ga-FAPI-04 demonstrated significantly higher uptake on PET and detected additional organ involvement compared to [^{18}F]FDG[45].

Other Gallium-68 based tracers that have been used with very promising results in the imaging of auto-immune disease, include ^{68}Ga-DOTA-TOC/NOC/TATE[47], ^{68}Ga-RGD[48] and ^{68}Ga-DOTA-Siglec-9[39] (Fig. 4).

A systematic review of 38 observational studies by Anzola et al.[32] evaluated somatostatin receptor-based imaging in chronic inflammatory diseases that included RA, sarcoidosis, cardiac allografts, atherosclerotic plaques, Sjogren's, IPF and Graves' disease. Unfortunately, due to the heterogenous nature of the included studies, data could not be pooled for statistical analysis in any meaningful way[32] (Fig. 5).

A study by Shamim and colleagues[49] compared the use of ^{68}Ga-DOTANOC PET in nineteen patients with Rheumatoid arthritis to ^{99m}Tc-MDP and found similar detection rates. However, the PET tracer offered the added advantage of potential theranostic approaches in patients that are refractory to disease-modifying antirheumatic drugs[49].

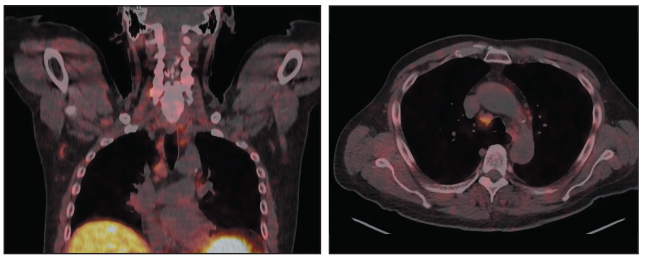


Figure 5. Demonstrates inflammatory lymph node accumulation on ^{68}Ga-DOTATATE.

Other studies have targeted the extensive neovascularization of the synovial membrane and the upregulation of integrin subtypes α5vβ1 and αvβ3. Dietz and colleagues[50] also evaluated the use of ^{68}Ga-NODAGA-RGDyk PET in rheumatoid arthritis[50] and found better target to background ratios when compared to FDG. Other promising approaches have included the use of ^{68}Ga-DOTA-Siglec-9 following safety and feasibility studies.

CONCLUDING REMARKS

Numerous infection and inflammation tracers have been developed, but what would the ideal tracer look like?

Established tracers like [^{18}F]FDG, ^{99m}Tc/^{111}In-WBC and ^{67}Gallium-citrate have an excellent track record in both infection- and inflammation imaging but are slowly falling out of favour (mainly) due to cumbersome logistics, costs, non-specificity, suboptimal normal biodistribution and unfavourable dosimetry. These are some of the important lessons to consider when developing future tracers.

Pre-clinical research should be optimized in such a way that the development of infection probes is aimed at including a broader spectrum of infective organisms, rather than a single infective agent. Targeting individual infective organisms make for great specificity, but practical application becomes difficult as the imaging tool must be chosen based on an already strong suspicion, which is often not the case in clinical practice. A broader approach that targets the microenvironment of the disease process may be more feasible and is highlighted by the rapidly expanding applications of FAPI in infection- and inflammation, without the need for differentiation between these processes.

Ideally, normal tracer bio-distribution should allow for easy detection of pathology within the brain, lungs, cardiovascular and musculoskeletal system (as some of the most frequently affected sites). It should also allow for detection within excretory organs (liver, bowel, and kidneys) without the need for additional imaging at delayed time points. A reasonable half-life, which allows for the logistics of off-site transport without resulting in unnecessary radiation dose received, is preferable. Versatility in terms of both SPECT and PET/CT imaging possibilities provides another big advantage. Referring physicians prefer studies

that do not require any specific patient preparation, and which provides a same day answer. Nuclear physicians additionally require good target to background ratios with clear, standardised interpretation criteria. It is clearly easier to transition tracers that are already approved for other (oncological) indications into infection and inflammation imaging applications, since large bodies of evidence already exist to support efficacy and lack of side effects.

One of the other main considerations to ensure the successful transition of new tracers from the cold to the hot lab would be to seek to address an important clinical problem, rather than to find applications for existing tracers. When there is a significant clinical need, it drives increased demand for useful diagnostic tests that can timeously answer the clinical questions raised. Simultaneously, it would serve to increase knowledge and appreciation for nuclear medicine amongst clinicians as a first-choice modality, rather than a last resort option.

Some of the most promising newcomers to the field of infection and inflammation imaging include ^{68}Ga-FAPI, ^{68}Ga-CXCR-4, ^{68}Ga-RGD, ^{68}Ga-SSTR targeted imaging and ^{68}Ga-citrate. Of these, FAPI is certainly the one to keep an eye on, considering its many ideal characteristics together with its theranostic translation potential.

REFERENCES

1. Baker RE et al. Infectious disease in an era of global change. Nat. Rev. Microbiol. 2022; 20, 193-205.
2. Vorster M, Maes A, de Wiele CV, Sathekge M. Gallium-68. Nucl. Med. Commun. 2013; 34, 834-54.
3. Kuwert T, Schmidkonz C, Prante O, Schett G. Ramming A. FAPI PET Opens a New Window to Understanding Immune-Mediated Inflammatory Diseases. J. Nucl. Medicine. 2022; 63, 1136-7.
4. Kratochwil C et al. 68Ga-FAPI PET/CT: Tracer Uptake in 28 Different Kinds of Cancer. J. Nucl. Med. 2019; 60, 801-5.
5. Bentestuen M, Al-Obaydi N, Zacho HD. FAPI-avid nonmalignant PET/CT findings: An expedited systematic review. Semin. Nucl. Medicine (2023) doi:10.1053/j.semnuclmed.2023.02.001.
6. Gege Z, Xueju W. Bin J. Head-To-Head Comparison of 68 Ga-FAPI PET/CT and FDG PET/CT for the Detection of Peritoneal Metastases: Systematic Review and Meta-Analysis. Am. J. Roentgenol. 2023; 220: 490-8.
7. Sollini M et al. State-of-the-art of FAPI-PET imaging: a systematic review and meta-analysis. Eur. J. Nucl. Medicine Mol. Imaging. 2021; 48: 4396-414.
8. Treglia G, Albano D. FAPI PET/CT in infectious, inflammatory, and rheumatological diseases: "watch it like a hawk" or "one swallow does not make a summer"? Eur. J. Nucl. Medicine Mol. Imaging. 2023; 50: 1848-50.
9. Mori Y et al. FAPI PET: Fibroblast Activation Protein Inhibitor Use in Oncologic and Nononcologic Disease. Radiology. 2023; 306, e220749.
10. Hoven AF van den et al. Current research topics in FAPI theranostics: a bibliometric analysis. Eur. J. Nucl. Medicine Mol. Imaging. 2023; 50, 1014-27.
11. Windisch P et al. Clinical results of fibroblast activation protein (FAP) specific PET for non-malignant indications: systematic review. EJNMMI Res. 2021; 11: 18.
12. Caobelli F. Nappi C. A spotlight on fibroblast-activated protein inhibitor (FAPI) cardiovascular imaging. Clin. Transl. Imaging. 2023; 11: 229-33.
13. Song W et al. 68Ga-FAPI PET visualize heart failure: from mechanism to clinic. Eur. J. Nucl. Medicine Mol. Imaging. 2023; 50: 475-85.
14. Varasteh Z et al. Molecular Imaging of Fibroblast Activity After Myocardial Infarction Using a 68Ga-Labeled Fibroblast Activation Protein Inhibitor, FAPI-04. J. Nucl. Med. 2019; 60, 1743-9.
15. Zhang M et al. [68Ga]Ga-DOTA-FAPI-04 PET/MR in patients with acute myocardial infarction: potential role of predicting left ventricular remodeling. Eur. J. Nucl. Med. Mol. Imaging 2023; 50, 839-48.
16. Notohamiprodjo S et al. Imaging of cardiac fibroblast activation in a patient after acute myocardial infarction using 68Ga-FAPI-04. J. Nucl. Cardiol. 2022; 29, 2254-61.
17. Finke D et al. Early Detection of Checkpoint Inhibitor-Associated Myocarditis Using 68Ga-FAPI PET/CT. Front. Cardiovasc. Med. 2021; 8, 614997.
18. Shi X, Lin X, Huo L, Li X. Cardiac fibroblast activation in dilated cardiomyopathy detected by positron emission tomography. J. Nucl. Cardiol. 2022; 29, 881-4.
19. Zacherl MJ et al. Molecular imaging of cardiac CXCR4 expression in a mouse model of acute myocardial infarction using a novel 68Ga-mCXCL12 PET tracer. J. Nucl. Cardiol. 2021; 28, 2965-75.
20. Li X, Rosenkrans ZT, Wang J, Cai W. PET imaging of macrophages in cardiovascular diseases. Am. J. Transl. Res. 2020; 12, 1491-514.
21. Kirienko M, Erba PA, Chiti A, Sollini M. Hybrid PET/MR in Infection and Inflammation: An Update About the Latest Available Literature Evidence. Semin. Nucl. Medicine. 2023; 53, 107-24.
22. Vorster M. Gallium-68 Labelled Radiopharmaceuticals for Imaging Inflammatory Disorders. Semin. Nucl. Med. 2023; 53, 199-212.
23. Dietz M et al. Imaging angiogenesis in atherosclerosis in large arteries with 68Ga-NODAGA-RGD PET/CT: relationship with clinical atherosclerotic cardiovascular disease. EJNMMI Res. 2021; 11: 71.
24. Sivapackiam J et al. Galuminox: Preclinical validation of a novel PET tracer for non-invasive imaging of oxidative stress in vivo. Redox Biol. 2020; 37, 101690.
25. Ndlovu H et al. [68Ga]Ga-NODAGAZOL uptake in atherosclerotic plaques correlates with the cardiovascular risk profile of patients. Ann. Nucl. Med. 2022; 36: 684-92.
26. Lu Y, Macapinlac HA. Advances in PET Imaging of Sarcoidosis. Curr. Cardiovasc. Imaging Rep. 2019; 12; 10.
27. Kaushik P et al. Comparison of 68Ga-DOTANOC PET/CT with cardiac MRI in patients with clinical suspicion of cardiac sarcoidosis. Ann. Nucl. Med. 2021; 35: 1058-65.
28. Bravo PE et al. Feasibility of somatostatin receptor-targeted imaging for detection of myocardial inflammation: A pilot study. J. Nucl. Cardiol. 2021; 28: 1089-99.
29. Bravo PE, Singh A, Carli MFD, Blankstein R. Advanced cardiovascular imaging for the evaluation of cardiac sarcoidosis. J. Nucl. Cardiol. 2019; 26: 188-99.
30. Meester EJ et al. Imaging inflammation in atherosclerotic plaques, targeting SST2 with [111In]In-DOTA-JR11. J. Nucl. Cardiol. 2021; 28, 2506-13.
31. Baghel V, Kaushik P, Seth S, Patel C. Somatostatin analogue scintigraphy in myocardial inflammation: An interesting image. J. Nucl. Cardiol. 2020; 27, 2436-7.
32. Anzola LK et al. Somatostatin receptor imaging by SPECT and PET in patients with chronic inflammatory disorders: a

systematic review. Eur. J. Nucl. Med. Mol. Imaging. 2019; 46: 2496-513.
33. Broens B et al. Novel tracers for molecular imaging of interstitial lung disease: A state of the art review. Autoimmun. Rev. 2022; 21: 103202.
34. Bergmann C et al. 68Ga-FAPI-04 PET-CT for molecular assessment of fibroblast activation and risk evaluation in systemic sclerosis-associated interstitial lung disease: a single-centre, pilot study. Lancet Rheumatol. 2021; 3, e185-e194.
35. Hao B et al. [^{18}F]FDG and [68Ga]Ga-DOTA-FAPI-04 PET/CT in the evaluation of tuberculous lesions. Eur. J. Nucl. Medicine Mol. Imaging. 2021; 48: 651-2.
36. Zhao L, Pang Y, Sun L, Lin Q, Chen H. Increased 68Ga-FAPI Uptake in the Pulmonary Cryptococcus and the Postradiotherapy Inflammation. Clin. Nucl. Medicine. 2022; 47: 243-5.
37. Sviridenko A et al. Enhancing Clinical Diagnosis for Patients With Persistent Pulmonary Abnormalities After COVID-19 Infection. Clin. Nucl. Medicine. 2022; 47: 1026-9.
38. Bresser PL, Reed J, Sathekge MM, Vorster M. 68Ga-nitroimidazole PET/CT imaging of hypoxia in tuberculosis: A case series. J. Méd. Radiat. Sci. 2022; 69: 518-24.
39. Retamal J et al. Feasibility of (68)Ga-labeled Siglec-9 peptide for the imaging of acute lung inflammation: a pilot study in a porcine model of acute respiratory distress syndrome. Am. J. Nucl. Med. Mol. imaging. 2015; 6: 18-31.
40. Tetikkurt C et al. Diagnostic utility of 68Ga-citrate and 18FDG PET/CT in sarcoidosis patients. Monaldi Arch. Chest Dis. 2020; 90.
41. Vorster M, Maes A, Wiele C, van de Sathekge M. 68Ga-citrate PET/CT in tuberculosis: a pilot study. Q. J. Nucl. Med. Mol. Imaging. 2019; 63: 48-55.
42. Xu T, Chen Y. Research Progress of [68Ga]Citrate PET's Utility in Infection and Inflammation Imaging: a Review. Mol. Imaging Biol. 2020; 22: 22-32.
43. Wang Y et al. Diagnostic efficiency of [68 Ga]Ga-DOTA-FAPI-04 in differentiating periprosthetic hip joint infection and aseptic failure. Eur. J. Nucl. Medicine Mol. Imaging. 2023; 50: 1919-28.
44. Wang Y et al. Different uptake patterns of 68Ga-FAPI in aseptic loosening and periprosthetic joint infection of hip arthroplasty: A case series and literature review. Frontiers Medicine. 2022; 9: 1014463.
45. Schmidkonz C et al. Disentangling inflammatory from fibrotic disease activity by fibroblast activation protein imaging. Ann. Rheum. Dis. 2020; 79: 1485-91.
46. Luo Y et al. Fibroblast Activation Protein-Targeted PET/CT with 68 Ga-FAPI for Imaging IgG4-Related Disease: Comparison to [^{18}F]FDG PET/CT. J. Nucl. Medicine. 2020; 62: 266-71.
47. Arora S et al. Graves' Ophthalmopathy on 68Ga-DOTANOC Positron Emission Tomography/Computed Tomography. Indian J. Nucl. Med. : IJNM : Off. J. Soc. Nucl. Med, India. 2019; 34: 338-40.
48. Notni J et al. In vivo imaging of early stages of rheumatoid arthritis by α5β1-integrin-targeted positron emission tomography. EJNMMI Res. 2019; 9: 87.
49. Shamim SA et al. Comparison of ^{99m}Tc-methyl diphosphonate bone scintigraphy and 68Ga-DOTANOC PET/computed tomography in articular manifestation of rheumatoid arthritis. Nucl. Med. Commun. 2022; 43: 428-32.
50. Dietz M et al. Imaging of αvβ3 integrin expression in rheumatoid arthritis with [68Ga]Ga-NODAGA-RGDyk PET/CT in comparison to [^{18}F]FDG PET/CT. Médecine Nucléaire. 2021; 45: 293-5.