



The right tracer for the right infection: choosing biology over technology in infection imaging

Luca Filippi¹ · Orazio Schillaci¹

Received: 27 July 2026 / Accepted: 25 August 2026

© The Author(s), under exclusive licence to Italian Association of Nuclear Medicine Molecular Imaging and Therapy (AIMN) 2026

Inflammation is not a single biological entity. It encompasses dynamic and overlapping processes involving different immune-cell populations, chemokine axes, vascular responses, tissue remodeling, and repair. Consequently, molecular imaging techniques described under the broad umbrella of “imaging inflammation” may visualize fundamentally different biological components of the inflammatory response. This distinction becomes particularly relevant when emerging targeted molecular PET tracers are directly compared with established leukocyte-based imaging approaches.

In a recently published study, Zorba et al. evaluated [⁶⁸Ga]Ga-Pentixafor PET/CT in patients with suspected chronic bone and soft tissue infections and compared its diagnostic performance with conventional scintigraphic imaging, including [^{99m}Tc]Tc-HMPAO-labeled leukocyte scintigraphy (LLS) [1]. The authors reported 100% sensitivity for [⁶⁸Ga]Ga-Pentixafor PET/CT (95% CI, 84–100%), based on 21 infected foci in 20 patients, and an overall accuracy of 95%. Although accuracy and AUC were numerically higher with CXCR4 PET, the difference in AUC between modalities did not reach statistical significance ($p=0.07$). These preliminary findings support the potential clinical value of CXCR4-targeted PET/CT while highlighting the uncertainty associated with the small sample size.

First, from a cellular and immunopathological perspective, comparing [⁶⁸Ga]Ga-Pentixafor directly with LLS introduces an underlying biological asymmetry that requires careful interpretation. In vitro and in vivo models have established that LLS primarily tracks neutrophilic granulocyte diapedesis and chemotaxis. Neutrophilic infiltration is a characteristic feature of many acute suppurative

and pyogenic infections, making LLS particularly useful in many acute, neutrophil-rich infectious processes [2]. Conversely, CXCR4 is expressed across multiple immune and non-immune cell populations, with particularly relevant expression in lymphocytes, monocytes/macrophages, and hematopoietic progenitor cells, although its expression is not restricted to these populations [3]. These cell populations may contribute to chronic immune responses, tissue remodeling, and repair, although the biological consequences of CXCR4 activation are highly context-dependent.

This immunobiological divergence is also illustrated by a case within the authors’ cohort. In a patient with dental implant infection and maxillary osteomyelitis, histopathological examination revealed necrotizing inflammation dominated by neutrophilic abscesses. LLS demonstrated intense accumulation, whereas [⁶⁸Ga]Ga-Pentixafor showed milder uptake. The authors hypothesized that necrosis-related hypoperfusion may have contributed to reduced tracer delivery and/or limited recruitment of CXCR4-expressing cells, while preserved neutrophil diapedesis allowed ongoing LLS accumulation. Thus, rather than indicating intrinsic superiority of one technique, this finding highlights how the inflammatory cellular composition and local microenvironment may influence the relative performance of different tracers.

Additional mechanistic insights emerge when examining the false-positive findings across both modalities. Overall, scintigraphy yielded three false-positive cases compared with two for CXCR4 PET. Importantly, two of these false-positive findings (i.e., an acute fracture site and Charcot neuroarthropathy) were shared limitations of both techniques, displaying only mild, low-level tracer accumulation (e.g., SUVmax of 1.7–2.8 and TBR of 2.5–2.8 for CXCR4 PET). Rather than highlighting a modality-specific pitfall of [⁶⁸Ga]Ga-Pentixafor, these cases reflect shared challenges of imaging non-infectious tissue remodeling and sterile inflammation. In contrast, the most informative discriminating case was an intramedullary nail, where reactive

✉ Luca Filippi
luca.filippi@uniroma2.it

¹ Department of Biomedicine and Prevention, University of Rome Tor Vergata, Via Montpellier, 1, Rome 00133, Italy

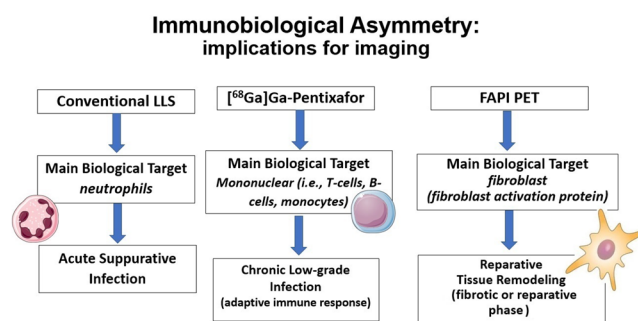


Fig. 1 Schematization of the potential complementary role of labeled leukocyte scintigraphy (LLS), CXCR4-targeted [^{68}Ga]Ga-Pentixafor and FAPI PET, respectively, in the various phases of infectious processes. Adapted from Servier Medical Art (<https://smart.servier.com>), licensed under CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>).

marrow expansion caused a false-positive result on scintigraphy, whereas CXCR4 PET was correctly negative (despite bone marrow scintigraphy confirming marrow expansion). This finding underscores a broader potential distinction between imaging leukocyte accumulation and evaluating specific receptor availability, although direct histopathological confirmation remains necessary. Importantly, these biological considerations should be interpreted within the population actually studied. Because acute infections were excluded, the reported performance of CXCR4 PET is most directly applicable to chronic and relatively indolent infectious processes and should not be extrapolated to acute or acute-on-chronic infections without further validation. This distinction suggests that the clinical value of each technique may depend not only on the anatomical site of infection but also on the biological composition and temporal stage of the inflammatory response (Fig. 1).

Second, the methodological limitations of the source study warrant consideration. Beyond the small sample size, the inclusion was biased toward patients undergoing surgery or tissue sampling, introducing potential selection and verification biases. Furthermore, image interpretation and SUV measurements were derived via consensus without evaluating interobserver agreement, which limits the robustness and generalizability of the findings. Regarding the comparison arm, the authors utilized a modern hybrid SPECT/CT system, with diagnostic classification relying on established multi-tracer concordance protocols (combining bone, leukocyte, and, when indicated, bone marrow scintigraphy) alongside visual interpretation and descriptive grading. CXCR4 PET classification similarly relied on visual assessment, with quantitative metrics (SUVmax and TBR) providing complementary data. Over the last decade, clinical nuclear medicine has increasingly moved toward quantitative SPECT/CT, with dedicated reconstruction algorithms allowing standardized activity measurements analogous to

PET [4]. Emerging data indicate that quantitative leukocyte SPECT/CT can yield clinically valuable information, particularly in complex cases such as diabetic foot infection [5]. While quantitative SPECT/CT should not be viewed as a missing requirement for diagnostic accuracy in the cohort studied by Zorba et al. [1], incorporating fully quantitative SPECT/CT could represent a valuable methodological enhancement for future head-to-head prospective trials.

Third, the translational potential of [^{68}Ga]Ga-Pentixafor beyond musculoskeletal infection warrants careful consideration of its biodistribution and potential off-target uptake. The tracer displays rapid plasma clearance and predominantly renal elimination, with relatively low nonspecific background activity in many soft-tissue regions, although urinary activity may limit assessment of lesions close to the urinary tract [6]. This specific pharmacokinetic profile opens up a promising, yet largely unexplored, translational avenue: the non-invasive imaging of inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis. Traditionally, using LLS to evaluate active IBD has been severely limited by passive intraluminal leukocyte shedding, non-specific physiological bowel transit, and unpredictable hepatobiliary clearance, which frequently yield false-positive findings [7]. In this clinical context, [^{68}Ga]Ga-Pentixafor PET/CT could theoretically offer a molecular map of active transmural gut inflammation without the confounding factor of luminal excretion.

The potential role of CXCR4 imaging should also be considered alongside other emerging approaches to imaging inflammation and tissue remodeling, including fibroblast activation protein (FAP)-targeted PET. Whereas [^{68}Ga]Ga-Pentixafor may provide information related to CXCR4-expressing cellular components of inflammation, FAP-targeted tracers visualize activated fibroblasts and stromal remodeling [8]. This distinction may be relevant in chronic osteoarticular disease, in which active inflammation, tissue repair, and fibrosis can coexist. However, both approaches may demonstrate uptake in sterile inflammatory or reparative conditions, emphasizing that molecular specificity does not necessarily equate to disease specificity. Rather than seeking a universal inflammatory tracer, future studies should determine which biological component of a lesion is most informative for the clinical question at hand.

In conclusion, the study by Zorba et al. [1] represents an important step in the clinical evaluation of CXCR4-targeted PET/CT for chronic bone and soft tissue infections. Its findings should nevertheless be interpreted in light of the small and heterogeneous cohort, retrospective design, potential selection and verification bias related to the diagnostic workflow, and consensus image interpretation without assessment of interobserver variability. Moreover, the comparison with LLS should not be viewed simply as a technological

competition, because the two techniques interrogate partially distinct biological processes. Future prospective studies should compare CXCR4 PET/CT with fully quantitative labeled leukocyte SPECT/CT while integrating histopathological characterization of the inflammatory infiltrate. Defining the clinical settings in which neutrophil-targeted and CXCR4-targeted imaging diverge may ultimately provide greater biological and clinical insight than establishing whether one modality should replace the other.

Acknowledgements None.

Author contributions L.F. and O.S. equally contributed to the manuscript.

Funding None.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare that they have no competing interests.

References

1. Denizmen Zorba D, Has Simsek D, Sanli Y et al (2026) Evaluating chronic bone and soft tissue infections with [68Ga]Ga-Pentixafor PET/CT: a head-to-head comparison with scintigraphy. *Eur J Nucl Med Mol Imaging* 53:3271–3282. <https://doi.org/10.1007/s00259-025-07749-3>
2. Censullo A, Vijayan T (2017) Using Nuclear Medicine Imaging Wisely in Diagnosing Infectious Diseases. *Open Forum Infect Dis* 4:ofx011. <https://doi.org/10.1093/ofid/ofx011>
3. Jacobson O, Weiss ID (2013) CXCR4 chemokine receptor overview: biology, pathology and applications in imaging and therapy. *Theranostics* 3:1–2. <https://doi.org/10.7150/thno.5760>
4. Filippi L, Schillaci O (2006) SPECT/CT with a hybrid camera: a new imaging modality for the functional anatomical mapping of infections. *Expert Rev Med Dev* 3:699–703. <https://doi.org/10.1586/17434440.3.6.699>
5. Park SB, Lim CH, Chun D-I et al (2024) The usefulness of quantitative 99mTc-HMPAO WBC SPECT/CT for predicting lower extremity amputation in diabetic foot infection. *Sci Rep* 14:9260. <https://doi.org/10.1038/s41598-024-59764-3>
6. Herrmann K, Lapa C, Wester H-J et al (2015) Biodistribution and Radiation Dosimetry for the Chemokine Receptor CXCR4-Targeting Probe⁶⁸Ga-Pentixafor. *J Nucl Med* 56:410–416. <https://doi.org/10.2967/jnumed.114.151647>
7. Filippi L, Biancone L, Petruzzello C, Schillaci O (2006) Tc-99m HMPAO-Labeled Leukocyte Scintigraphy With Hybrid SPECT/CT Detects Perianal Fistulas in Crohn Disease. *Clin Nucl Med* 31:541–542. <https://doi.org/10.1097/01.rlu.0000233082.89996.3a>
8. Zhou Y, Hou Y, Yin C et al (2026) FAPI PET in the Diagnosis and Management of Inflammatory Diseases: Clinical Value and Future Perspectives. *Clin Nucl Med* 51:35–43. <https://doi.org/10.1097/RLU.0000000000006175>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.