European Journal of Nuclear Medicine and Molecular Imaging (2022) 49:3610–3612
https://doi.org/10.1007/s00259-022-05857-y

EDITORIAL

Unnatural amino acids offer new hope for accurate bacterial infection PET imaging in prosthetic joint infection

Peter J. H. Scott[1]

Published online: 2 June 2022

Bacterial infections remain a significant cause of morbidity and mortality. Alone, they are responsible for millions of deaths per year, and with the continuing emergence of antibiotic resistant superbugs, the problem remains a serious threat to human health and well-being. As such, diagnostic procedures that allow accurate diagnosis of a bacterial infection as early as possible are critically important in the eternal battle between humans and microbes. Despite this need, existing methods (e.g., magnetic resonance imaging, computed tomography, ^{67}Ga-citrate single photon emission computed tomography, ^{18}F-fludeoxyglucose ([^{18}F]FDG) positron emission tomography (PET)) come up short, particularly if early in an infection's incubation period. White blood cell imaging is an alternative approach, but it is laborious to prepare ^{111}In-labeled WBCs and the procedure is operationally challenging.

This problem is particularly troublesome for prosthetic joint infection (PJI), where bacterial infections can be a quite common but serious complication. Given that PJI, particularly chronic infections, often present with nonspecific signs and symptoms that make definitive diagnosis difficult, imaging has been widely used to assist with diagnosis [1]. The problem is exacerbated further given the prevalence of other aseptic mechanisms of failure (e.g., osteolysis, aseptic loosening, polyethylene-related particle wear). [^{18}F]FDG PET, for example, struggles to distinguish PJI from some of these other failures, which is not surprising given that (intense) inflammation can be present in both aseptic failures (e.g., loosening), and infection [2]. Labeled WBCs on the other hand accumulate not only in areas of infection, but also in the bone marrow. The result is that imaging data often leaves radiologists and nuclear medicine physicians lacking confidence that an imaging finding is truly indicative of a PJI, and patients are oftentimes subjected to invasive tissue sampling anyway to achieve a definitive diagnosis. Since treatment of chronic PJI involves long-term broad-spectrum antibiotics, sometimes however, even tissue sampling can lead to culture-negative PJI.

These ongoing challenges have spurred efforts to develop imaging approaches which are specific for bacterial infection (for recent reviews of the topic, see 3, 4). PET imaging offers the possibility to noninvasively and specifically detect bacterial infections and, with an appropriate war chest of imaging agents, even distinguish between different types of bacteria (e.g., gram negative vs positive, antibiotic-resistant organisms), and both predict and monitor response to therapy. One extremely promising approach to developing imaging agents for bacterial infections capitalizes on differences between mammalian and bacterial physiology and biochemistry, and has involved radiolabeling of small molecules exclusively metabolized by bacteria (Fig. 1). One strategy for developing pathogen-specific PET imaging agents has targeted carbohydrates that are not efficiently metabolized by humans, but which can be metabolized by bacteria, including ^{18}F-labeled maltotriose [5, 6] and [^{18}F]2-deoxy-2-^{18}F-fluorosorbitol [7, 8].

A related strategy that has shown promise is labeling D-amino acids [9, 10]. While L-amino acids are building blocks of proteins in most cells, their unnatural D-amino acid counterparts are preferentially incorporated into bacterial cell walls during peptidoglycan biosynthesis. Capitalizing on this difference, David Wilson's laboratory at the University of California San Francisco is working on labeling a series of unnatural amino acids for infection imaging, including D-[^{11}C]alanine [11] and D-methyl-[^{11}C]-methionine (D-^{11}C-Met) [12]. In the case of D-^{11}C-Met, the team has previously reported a high enantiomeric excess in-loop radiosynthesis of the agent from the D-homocysteine precursor [12], and shown that for both gram-positive and

This article is part of the Topical Collection on Infection and Inflammation

✉ Peter J. H. Scott
pjhscott@umich.edu

[1] Department of Radiology, University of Michigan, Ann Arbor, MI 48109, USA

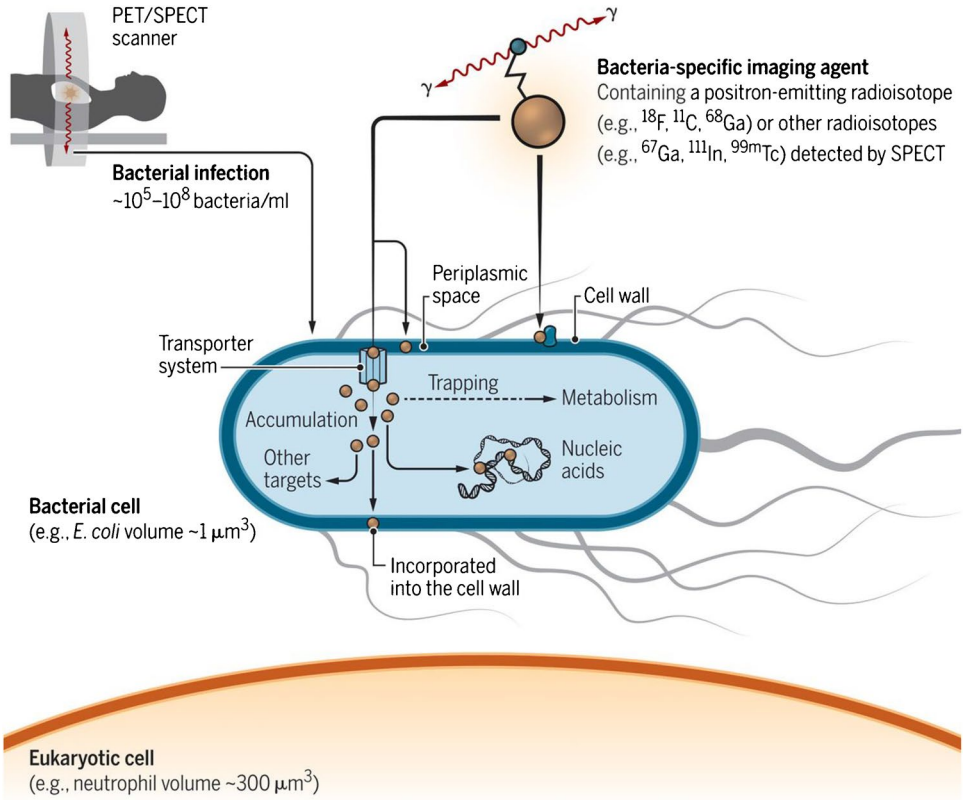

Fig. 1 Bacteria-specific PET and SPECT imaging tools. Reprinted from [3] with permission of AAAS

gram-negative bacteria, it can distinguish active infection from sterile inflammation in a murine model [13].

Building on these encouraging preclinical results, the team has now successfully translated D-^{11}C-Met for clinical use. In this issue of *the European Journal of Nuclear Medicine and Molecular Imaging*, Ohliger and Wilson describe biodistribution, radiation dosimetry, and initial human experience imaging patients with suspected prosthetic joint infection using D-^{11}C-Met [14]. In this first-in-human study, six healthy volunteers (3 M/3F) and five patients with suspected PJI received D-^{11}C-Met PET-MRI scans following dosing with 614.5 ± 100.2 MBq. The agent had low effective doses (0.0036 ± 0.00065 mSv/MBq and 0.0046 ± 0.00066 mSv/MBq for males and females, respectively), lower than L-^{11}C-Met (0.0052 ± 0.00045 mSv/MBq) which is a widely used oncology imaging agent. Continued uptake was observed in the liver, likely due to its ability to metabolize unnatural amino acids.

D-^{11}C-Met was well tolerated in all subjects (no adverse events were recorded) and, importantly, had low background in both organs with resident micro-flora as well as target organs in the muscoskeletal system. A limitation of the study is that arterial blood sampling was not conducted. Nevertheless, the investigators were able to apply a two-tissue compartment model by using the femoral artery (hip) or popliteal artery (knee) to derive image-based arterial input functions. For proof-of-concept, the team tested D-^{11}C-Met PET-MRI in five patients with suspected PJI, and compared tracer uptake in the affected joint to the non-affected contra-lateral joint.

Quantitative image analysis revealed that D-^{11}C-Met showed asymmetrical uptake in areas of suspected PJI compared to the unaffected contra-lateral joint in all five patients. Maximum uptake was observed 25 min post-injection of the imaging agent, and both SUV_{max} and SUV_{peak} showed significant increase in uptake in sites of suspected infection. Uptake was about 1.5 times in joints with suspected infection than unaffected joints. Kinetic analysis allowed determination of four rate constants, with the authors hypothesizing that a k_4 value > 0 is indicative of reversible binding. Regions of suspected infection were found to have both larger distribution volumes and higher binding potentials than the corresponding unaffected joints.

While there are limitations in this work, including a small sample size and the fact that many of the PJI subjects had been on long term antibiotic treatment (often leading to negative tissue cultures), these promising initial results from one of the leading groups in bacterial infection PET imaging create excitement for the future of the labeled D-amino acid approach. With a plethora of unnatural amino acids available for radiolabeling, one also has to ask the question about what else could be imaged using this strategy? Future studies with D-^{11}C-Met need to better understand tracer accumulation patterns, and the hope is that the authors can validate

target engagement and provide proof of efficacy by scanning patients with higher bacterial burden, and correlating PET data with histopathologic and microbiologic verification.

Declarations

Ethics approval Institutional Review Board approval was not required because the paper is an Editorial.

Consent to participate Not applicable.

Conflict of interest The author declares no competing interests.

References

1. Glaudemans AWJM, et al. Leukocyte and bacteria imaging in prosthetic joint infection. Eur Cell Mater. 2013;25:61–77.
2. Love C, Tomas MB, Tronco GG, Palestro CJ. FDG PET of infection and inflammation. Radiographics. 2005;25:1357–68.
3. Ordonez AA, Sellmyer MA, Gowrishankar G, et al. Molecular imaging of bacterial infections: overcoming the barriers to clinical translation. Sci Transl Med. 2019;11:eaax8251.
4. Auletta S, Varani M, Horvat R, Galli F, Signore A, Hess S. PET radiopharmaceuticals for specific bacteria imaging: a systematic review. J Clin Med. 2019;8:197.
5. Gowrishankar G, Hardy J, Wardak M, et al. Specific imaging of bacterial infection using 6″-^{18}F-fluoromaltotriose: a second-generation PET tracer targeting the maltodextrin transporter in bacteria. J Nucl Med. 2017;58:1679–84.
6. Axer A, Hermann S, Kehr G, Clases D, Karst U, Fischer-Riepe L, Roth J, Fobker M, Schafers M, Gilmour R, Faust A. Harnessing the maltodextrin transport mechanism for targeted bacterial imaging: structural requirements for improved in vivo stability in tracer design. ChemMedChem. 2018;13:241–50.
7. Li J, Zheng H, Fodah R, Warawa JM, Ng CK. Validation of 2–^{18}F-Fluorodeoxysorbitol as a potential radiopharmaceutical for imaging bacterial infection in the lung. J Nucl Med. 2018;59:134–9.
8. Yao S, Xing H, Zhu W, et al. Infection imaging with ^{18}F-FDS and first-in-human evaluation. Nucl Med Biol. 2016;43:206–14.
9. Neumann KD, Villanueva-Meyer JE, Mutch CA, et al. Imaging active infection in vivo using D-amino acid derived PET radiotracers. Sci Rep. 2017;7(1):7903.
10. Mota F, Jain SK. Flagging bacteria with radiolabeled D-amino acids. ACS Cent Sci. 2020;6:97–9.
11. Parker MFL, Luu JM, Schulte B, et al. Sensing living bacteria in vivo using D-alanine-derived ^{11}C radiotracers. ACS Cent Sci. 2020;6:155–65.
12. Stewart MN, Parker MFL, Jivan S, et al. High enantiomeric excess in-loop synthesis of D-[methyl-^{11}C]methionine for use as a diagnostic positron emission tomography radiotracer in bacterial infection. ACS Infect Dis. 2020;6:43–9.
13. Neumann KD, Villanueva-Meyer JE, Mutch CA, et al. Imaging active infection in vivo using D-amino acid derived PET radiotracers. Sci Rep. 2017;7(1):7903.
14. Polvoy I, Seo Y, Parker M et al. Imaging joint infections using D-methyl-^{11}C-methionine PET/MRI: initial experience in humans. Eur J Nucl Med Mol Imaging. 2002. https://doi.org/10.1007/s00259-022-05858-x.